TITLE OF THE INVENTION

(HALO-BENZO CARBONYL)HETEROCYCLO FUSED PHENYL P38 KINASE INHIBITING AGENTS

INS A1

BACKGROUND OF THE INVENTION

The present invention relates to compounds that inhibit the action of the p38 mitogen-activated protein kinase, a mammalian protein kinase that is involved in cell proliferation, cell response to stimuli, and cell death. In particular, this invention relates to heterocyclic compounds that are selective and potent inhibitors of the p38 mitogen-activated protein kinase. This invention also relates to pharmaceutical compositions containing such heterocyclic compounds that inhibit the p38 mitogen-activated protein kinase.

Related background

Mitogen-activated protein ("MAP") kinases mediate the surface-to-nucleus signal transduction in a cell. Protein kinases that activate and phosphorylate MAP are known as mitogen-activated protein kinase kinases ("MKK"). One such MKK specifically phosphorylates and activates the p38 MAP kinase ("p38") and is called MKK3. U.S. Patent Nos. 5,736,381 and 5,804,427 describe human mitogen-activated kinase kinase isoforms. International Publication No. 98/00539 describes a human gene encoding an MKK3-Interacting Protein.

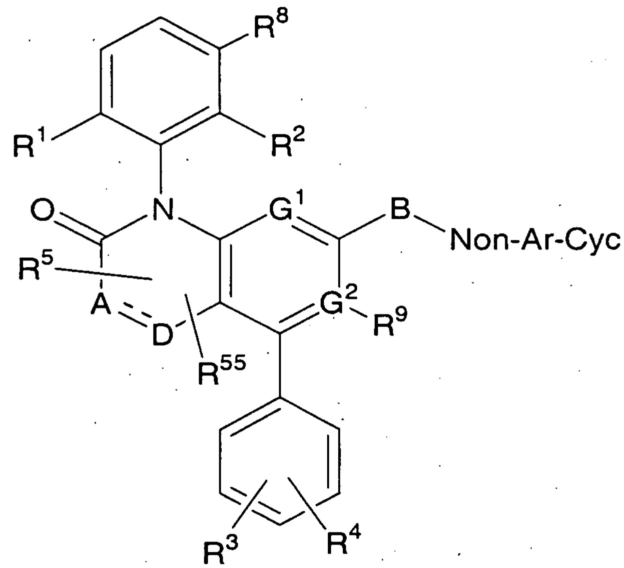
Xia et al., *Science*, 270, 1326-1331 (1995) describes the p38 signal transduction pathway as being activated by proinflammatory cytokines and environmental stress. MKK3 is described as being involved in transducing stress signals such as nerve growth factor mediated apoptosis in PC12 cells. It is believed that inhibition of p38 activity can provide relief from acute and chronic inflammation by blocking production of cytokines such as IL-1 and TNF, thereby inhibiting the production of proinflammatory cytokines such as IL-6 and IL-8. In particular, it is believed that p38 inhibitors block the synthesis of TNFα and IL-1β cytokines, thereby providing relief from inflammatory diseases such as arthritis. Accordingly, it would be desirable to provide novel compounds that are selective and potent inhibitors of the action of p38.

International Publication No. 97/22704 describes the mitogen-activated protein kinase kinase MEK6, which can stimulate phosphorylation and activation of

p38 substrates. International Publication Nos. 95/31451, 99/00357 and 98/27098 describe various inhibitors of p38. Nonetheless, there remains a great need to develop inhibitors of the action of p38 for various pharmaceutical and therapeutic applications.

SUMMARY OF THE INVENTION

Compounds described by the chemical formula (I) or pharmaceutically acceptable salts thereof:

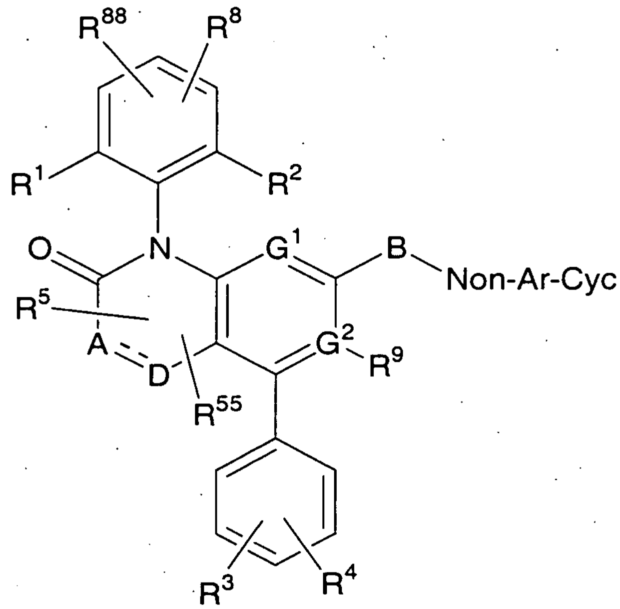


(I)

are inhibitors of p38.

DETAILED DESCRIPTION OF THE INVENTION

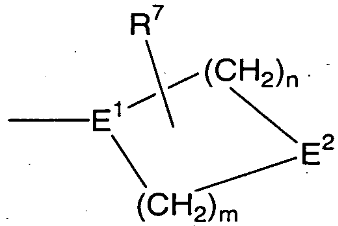
The present invention provides a compound that is an inhibitor of the action of p38, wherein the compound is described by the chemical formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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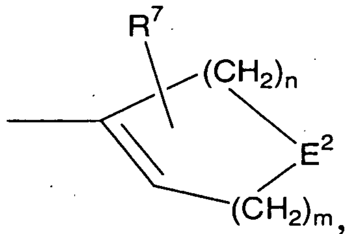

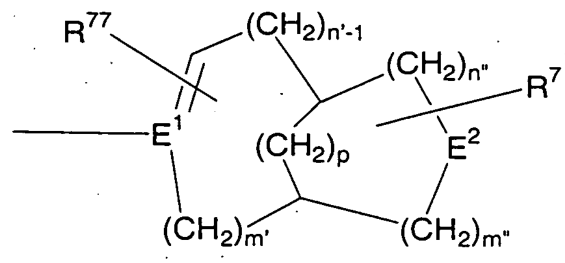

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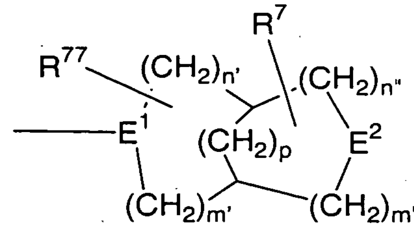

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A is N, O, NH, CH_2, or CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH, CH_2, N, or NH; optionally A and D are bridged by $-C_{1-4}$alkyl- to form a fused bicyclo ring with A and D at the bicyclo cusps;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted

with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

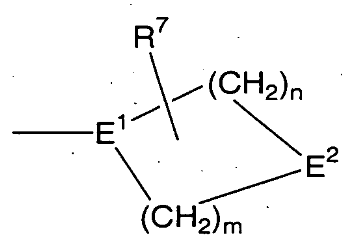
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In one aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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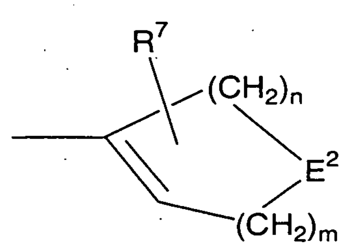

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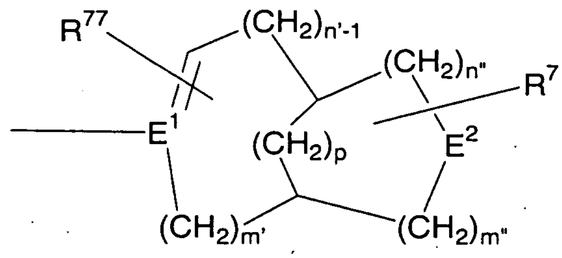

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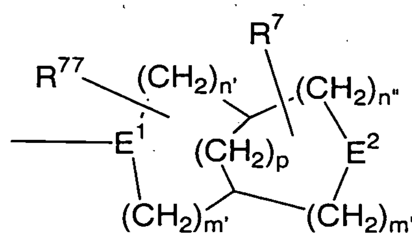


;

A is NH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_0-

4alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n'' = n;

m' + m'' = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

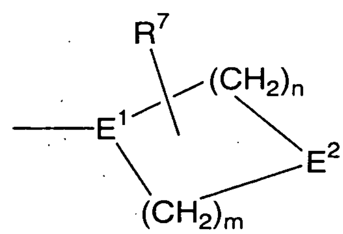
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In one embodiment of this aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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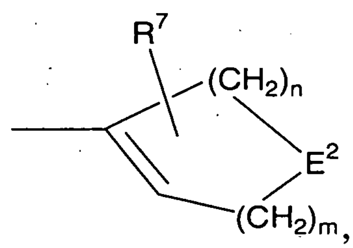

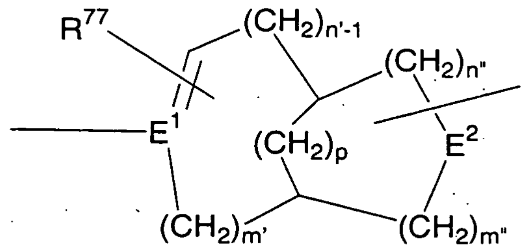

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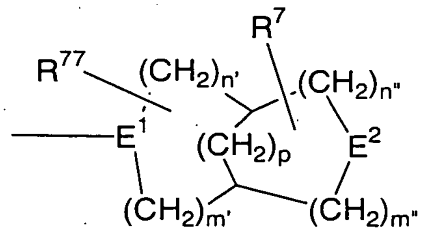


;

A is NH;

B is a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

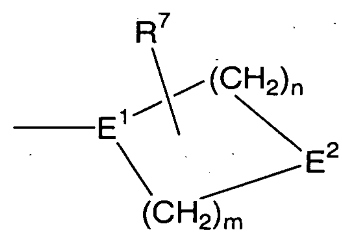
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of this aspect, the present invention the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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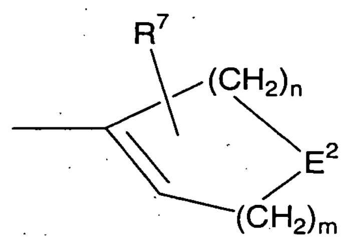

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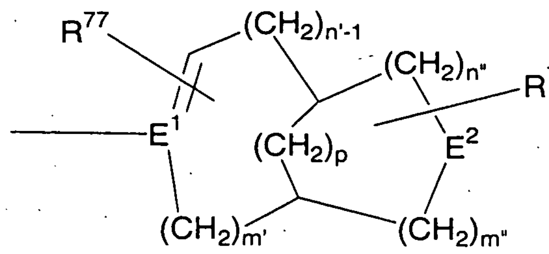

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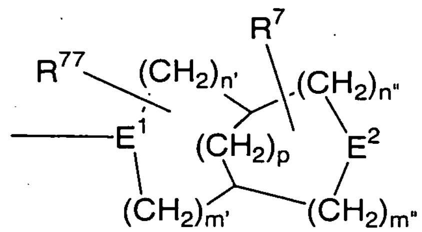

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A is NH;

B is $-C_{0-3}alkyl-O-C_{0-3}alkyl-$;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-C_{1-4}alkyl-N(C_{0-4}alkyl)-$ group, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)-$ group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

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n' + n" = n;

$m' + m'' = m$;

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m is 0, 1, 2, 3, or 4;

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p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

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In yet another embodiment of this aspect, the present invention provides the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

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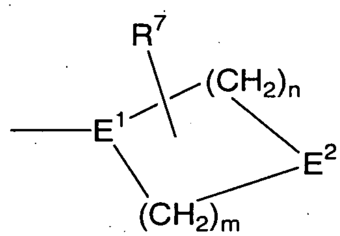

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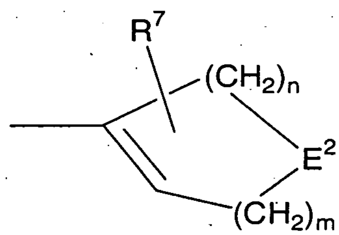

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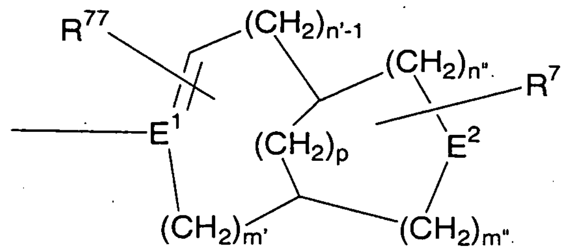

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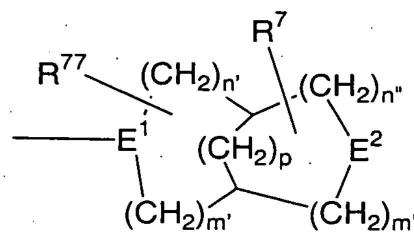

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A is NH;

B is $-C_{0-3}alkyl-C(O)-C_{0-3}alkyl$;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

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G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-C_{1-4}alkyl-N(C_{0-4}alkyl)-$ group, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)-$ group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

$n' + n'' = n$;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

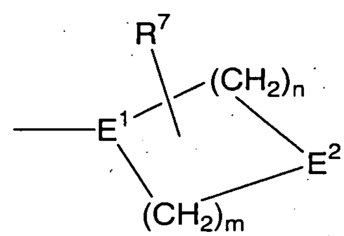
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of this aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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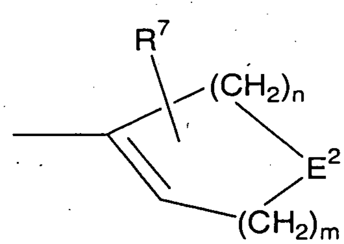

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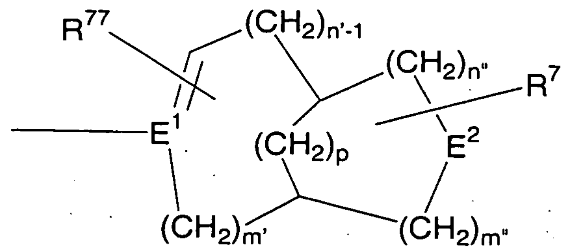

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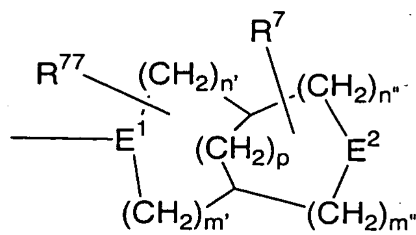

;

A is NH;

B is $-C_{1-6}$alkyl–;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}$alkyl);

G^2 is N, CH, or $C(C_{1-3}$alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}$alkyl–$N(C_{0-4}alkyl)$– group, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}$alkyl– group, pyridyl–$C_{0-4}$alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

$m' + m'' = m$;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

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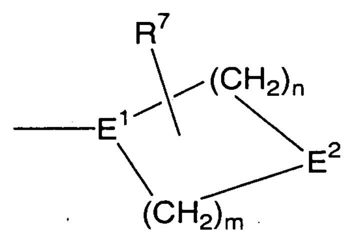
In still another embodiment of this aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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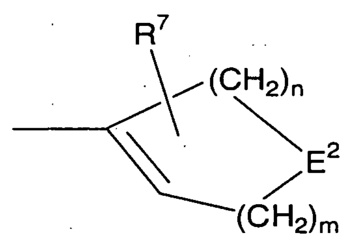

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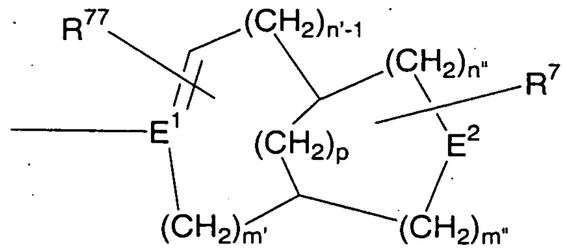

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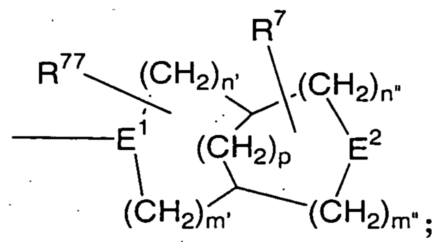


A is NH;

B is $-C_{0-3}$alkyl$-NH-C_{0-3}$alkyl$-$;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}$alkyl);

G^2 is N, CH, or $C(C_{1-3}$alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}$alkyl)$(C_{0-4}$alkyl)–C_{1-4}alkyl–$N(C_{0-4}$alkyl)– group, $-N(C_{0-4}$alkyl)$(C_{0-4}$alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}$alkyl)$(C_{0-4}$alkyl)–$(C_{0-4}$alkyl)C(O)$(C_{0-4}$alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $-N(C_{0-4}$alkyl)$(C_{0-4}$alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

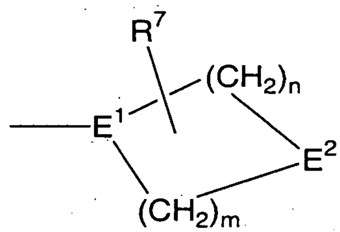
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In yet another embodiment of this aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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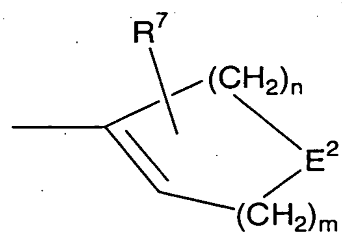

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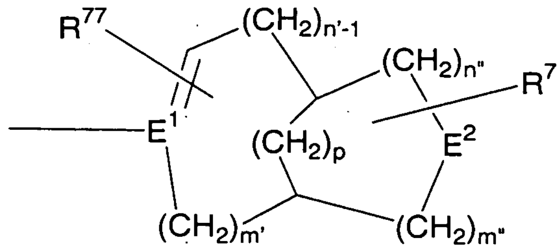

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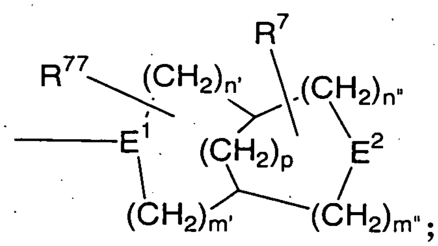


A is NH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-}

4alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

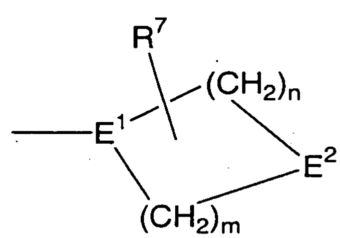
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In yet still another embodiment of this one aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



;

A is NH;

B is –$C_{1\text{-}6}$alkyl–, –$C_{0\text{-}3}$alkyl–O–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{3\text{-}7}$cycloalkyl–, –$C_{0\text{-}3}$alkyl–N($C_{0\text{-}3}$alkyl)–C(O)–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–S–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}$alkyl–$N(C_{0-4}alkyl)$– group, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}$alkyl– group, pyridyl–$C_{0-4}$alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n'' = n;

m' + m'' = m;

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p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

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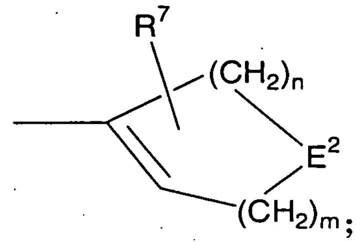
In still another embodiment of this one aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is NH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

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G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

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R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

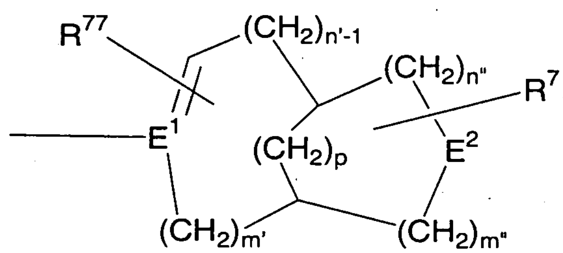
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of this one aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is NH;

B is –$C_{1\text{-}6}$alkyl–, –$C_{0\text{-}3}$alkyl–O–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{3\text{-}7}$cycloalkyl–, –$C_{0\text{-}3}$alkyl–N($C_{0\text{-}3}$alkyl)–C(O)–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–S–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N, CH, or C($C_{1\text{-}3}$alkyl);

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl– group, $C_{2\text{-}6}$alkenyl– group, $C_{4\text{-}6}$cycloalkyl-$C_{0\text{-}6}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–

$C_{1\text{-}4}$alkyl–N($C_{0\text{-}4}$alkyl)– group, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl) group, $C_{1\text{-}3}$alkyl–CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

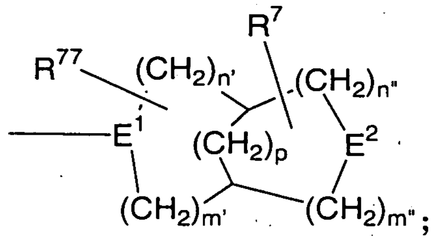
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of the first aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is NH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

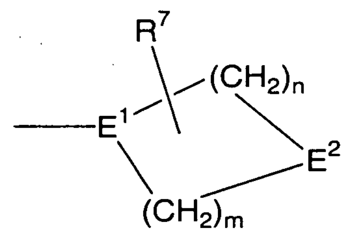
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In a second aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



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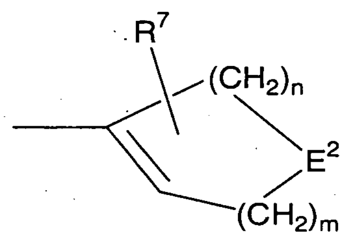

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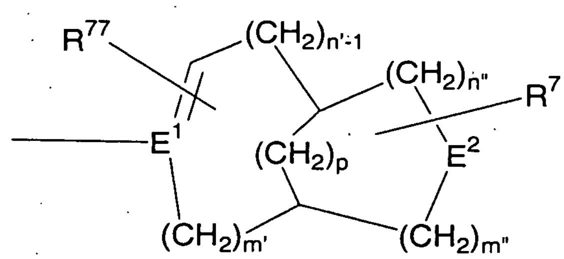
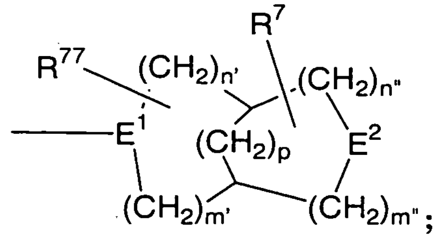


, or



A is N;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

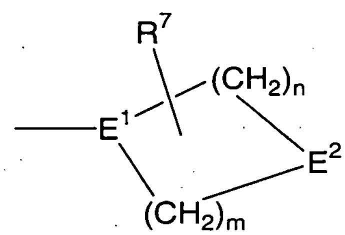
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of this second aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is


;

A is N;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–

$C(O)–O–C_{0-4}alkyl–$ group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)–$ group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, $C_{1-6}alkyl–CO–C_{0-4}alkyl–$, pyrrolidinyl–$C_{0-4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, $–C(O)-O(C_{0-4}alkyl)$, or $–C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

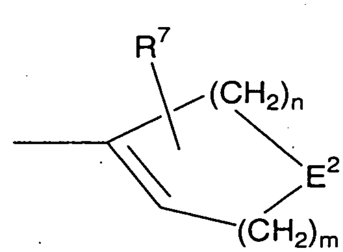
R^{88} and R^8 each is independently –CN, $–C_{0-4}$alkyl, $–C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $–C(O)-O-C_{0-4}$alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is $–C_{0-4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of this second aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is N;

B is $-C_{1-6}$alkyl$-$, $-C_{0-3}$alkyl$-O-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{3-7}$cycloalkyl$-$, $-C_{0-3}$alkyl$-N(C_{0-3}$alkyl$)-C(O)-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-S-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-PH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-C(O)-C_{0-3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}$alkyl);

G^2 is N, CH, or $C(C_{1-3}$alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl$-$ group, C_{2-6}alkenyl$-$ group, C_{4-6}cycloalkyl-C_{0-6}alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-C_{1-4}$alkyl$-N(C_{0-4}$alkyl$)-$ group, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)$ group, C_{1-3}alkyl$-CO-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-O-C(O)-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-C(O)-O-C_{0-4}$alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-(C_{0-4}$alkyl$)C(O)(C_{0-4}$alkyl$)-$ group, phenyl$-C_{0-4}$alkyl$-$ group, pyridyl$-C_{0-4}$alkyl$-$ group, pyrimidinyl$-C_{0-4}$alkyl$-$ group, pyrazinyl$-C_{0-4}$alkyl$-$ group, thiophenyl$-C_{0-4}$alkyl$-$ group, pyrazolyl$-C_{0-4}$alkyl$-$ group, imidazolyl$-C_{0-4}$alkyl$-$ group, triazolyl$-C_{0-4}$alkyl$-$ group, azetidinyl$-C_{0-4}$alkyl$-$ group, pyrrolidinyl$-C_{0-4}$alkyl$-$ group, isoquinolinyl$-C_{0-4}$alkyl$-$ group, indanyl$-C_{0-4}$alkyl$-$ group, benzothiazolyl$-C_{0-4}$alkyl$-$ group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being $-OH$, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl$-CO-C_{0-4}$alkyl$-$, pyrrolidinyl$-C_{0-4}$alkyl$-$, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, $-C(O)-O(C_{0-4}$alkyl$)$, or $-C(O)-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)$;

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

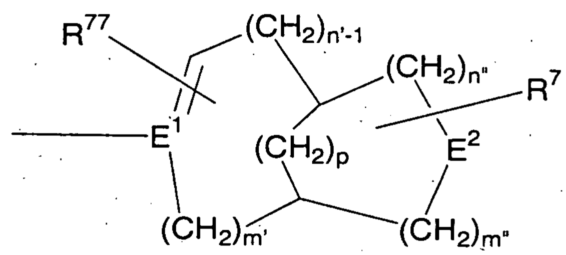
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of this second aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is N;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –S(O)2–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-}

4alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

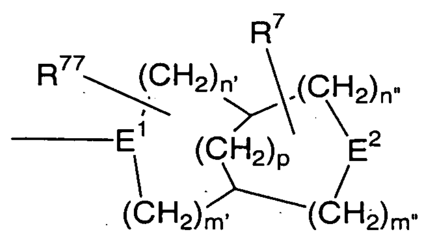
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of this second aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is N;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–

C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

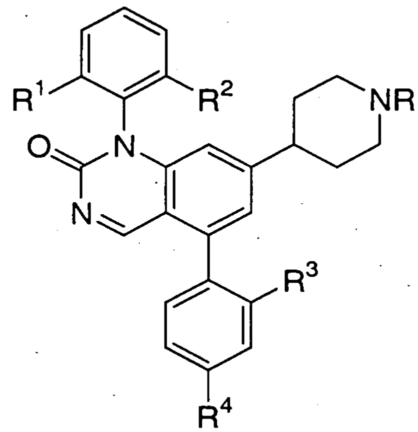
R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

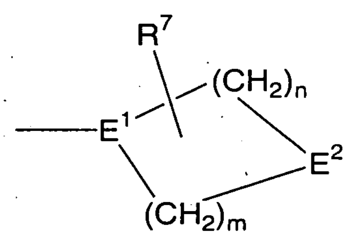
In one embodiment of this second aspect, the present invention provides a compound described by the chemical formula (IIIA) or a pharmaceutically acceptable salt thereof:



(IIIA)

In a third aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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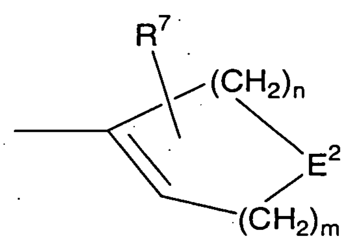

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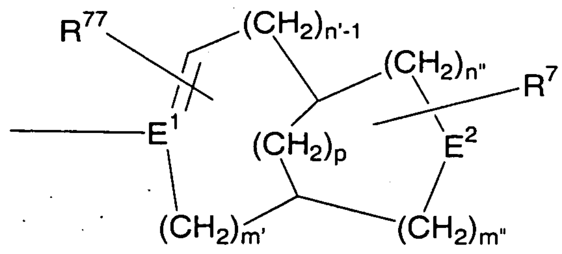
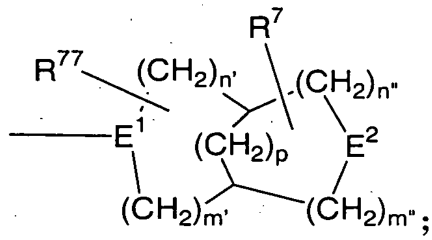


, or



A is O;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-}

4alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

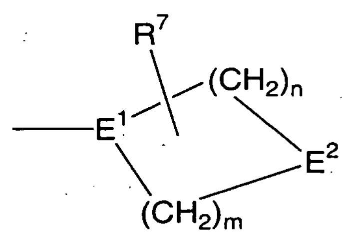
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the third aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



;

A is O;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}$alkyl–$N(C_{0-4}alkyl)$– group, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}$alkyl– group, pyridyl–$C_{0-4}$alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

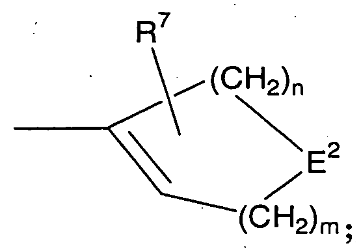
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the third aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



A is O;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

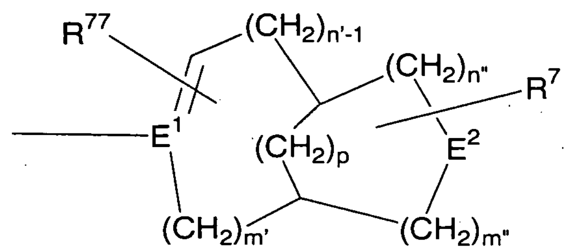
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the third aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



;

A is O;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –S(O)2–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–

C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

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n is 1, 2, 3, or 4;

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n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

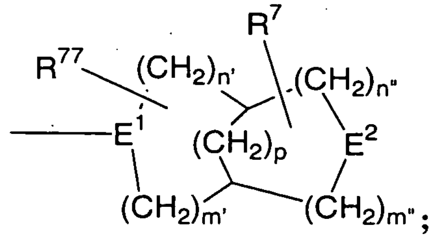
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the third aspect, the present invention provides a compound described by the chemical formula (I) or a pharmaceutically acceptable salt thereof wherein

Non-Ar-Cyc is



A is O;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

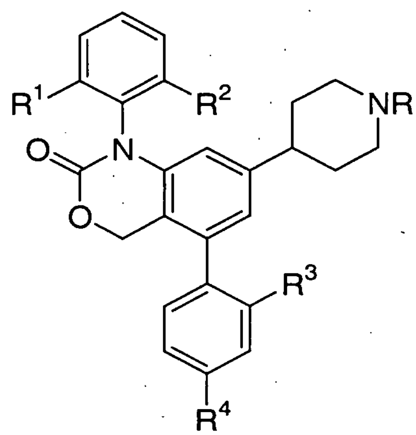
R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

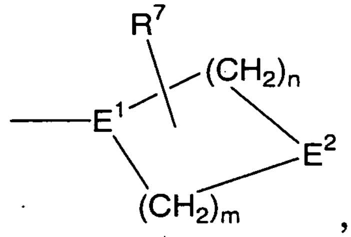
In one embodiment of this third aspect, the present invention provides a compound described by the chemical formula (IVA) or a pharmaceutically acceptable salt thereof:

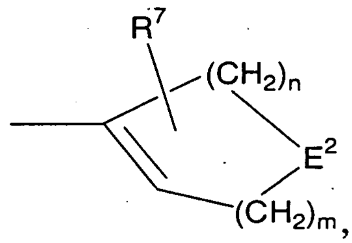


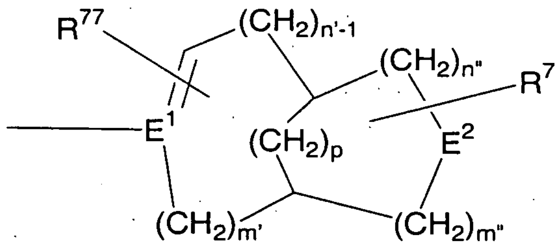
(IVA)

In a fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

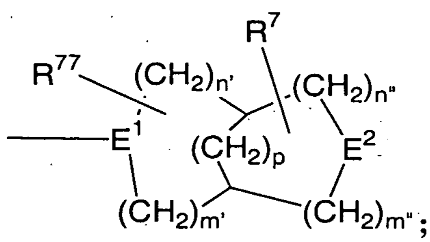
Non-Ar-Cyc is







, or



A is CH_2;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

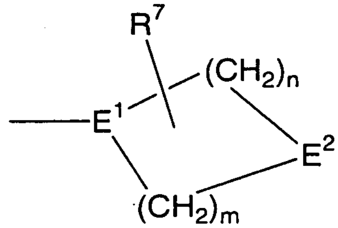
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In one embodiment of this fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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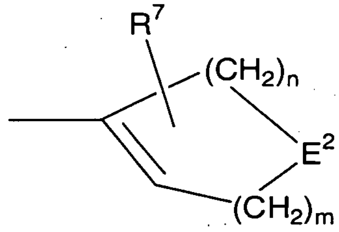

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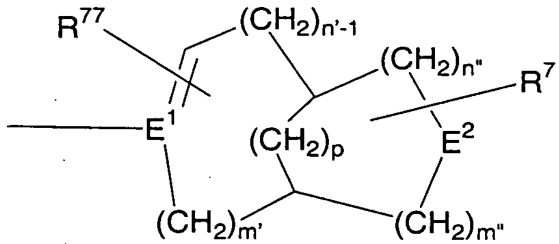

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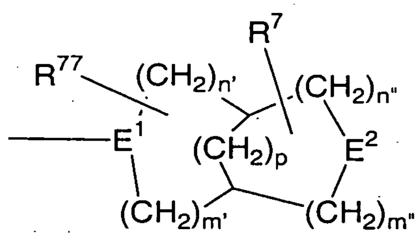


;

A is CH_2;

B is a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, $C_{1-6}alkyl$– group, $C_{2-6}alkenyl$– group, $C_{4-6}cycloalkyl$-$C_{0-6}alkyl$– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}alkyl$–$N(C_{0-4}alkyl)$– group, –$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, $C_{1-3}alkyl$–

CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

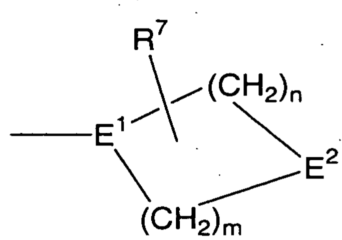
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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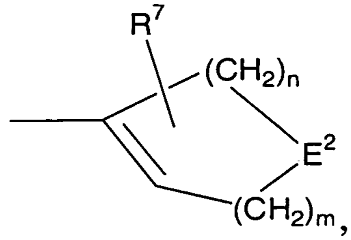

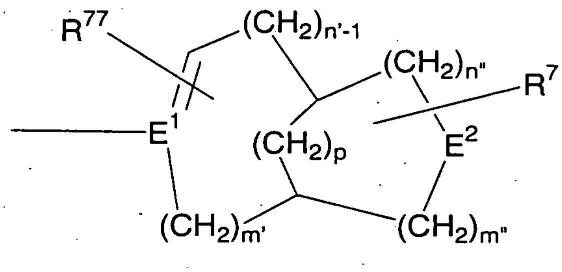

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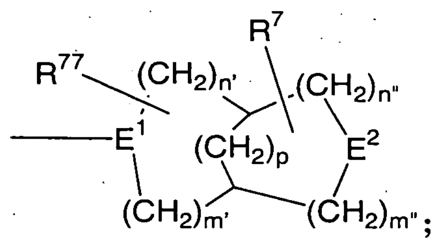


A is CH_2;

B is $-C_{0-3}$alkyl$-O-C_{0-3}$alkyl$-$;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}$alkyl);

G^2 is N, CH, or $C(C_{1-3}$alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}$alkyl)$(C_{0-4}$alkyl)–C_{1-4}alkyl–$N(C_{0-4}$alkyl)– group, $-N(C_{0-4}$alkyl)$(C_{0-4}$alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}$alkyl)$(C_{0-4}$alkyl)–$(C_{0-4}$alkyl)C(O)$(C_{0-4}$alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-}

4alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

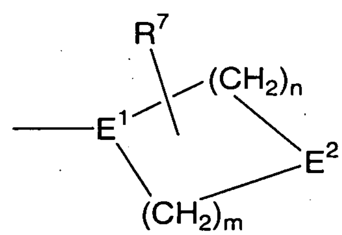
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH_2;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–

C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

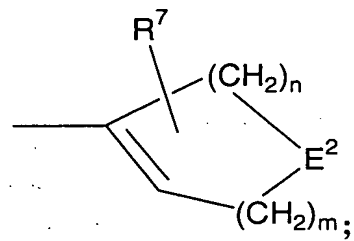
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of the fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is CH_2;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

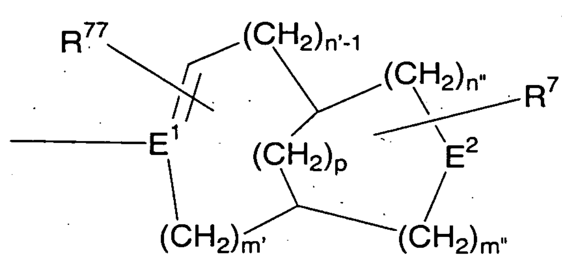
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In yet another embodiment of the fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH_2;

B is –$C_{1\text{-}6}$alkyl–, –$C_{0\text{-}3}$alkyl–O–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{3\text{-}7}$cycloalkyl–, –$C_{0\text{-}3}$alkyl–N($C_{0\text{-}3}$alkyl)–C(O)–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–S–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

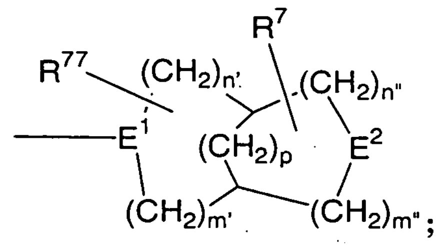
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fourth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is CH_2;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

$n+m$ is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

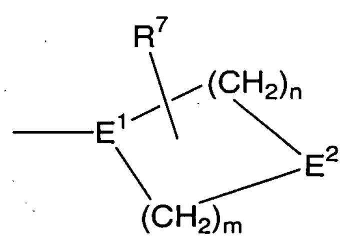
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In a fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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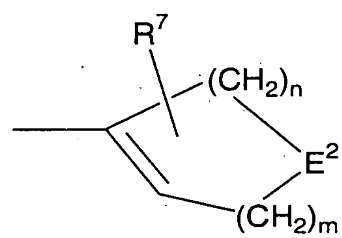

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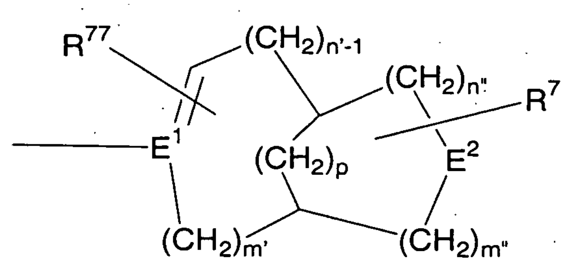

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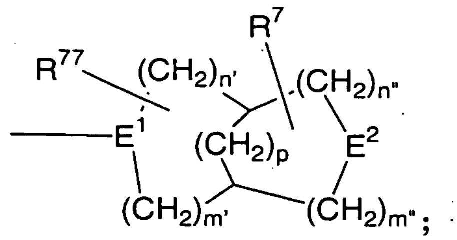


A is CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

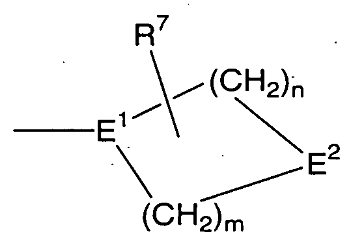
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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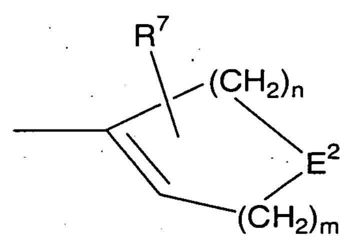

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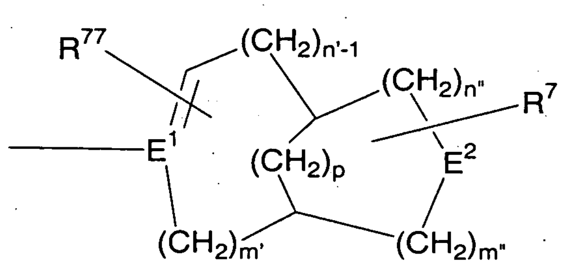

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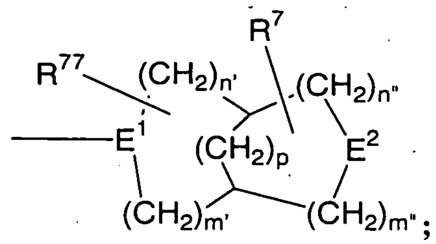


A is CH;

B is a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}$alkyl–$N(C_{0-4}alkyl)$– group, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}$alkyl– group, pyridyl–$C_{0-4}$alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

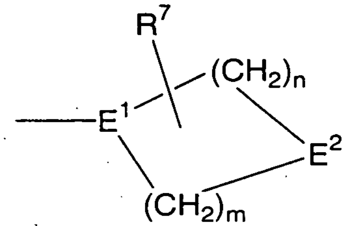
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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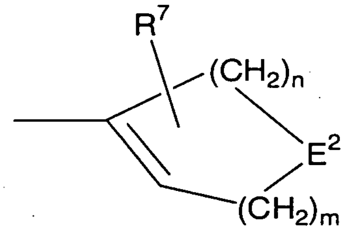

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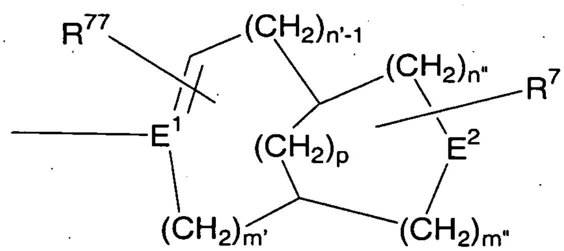

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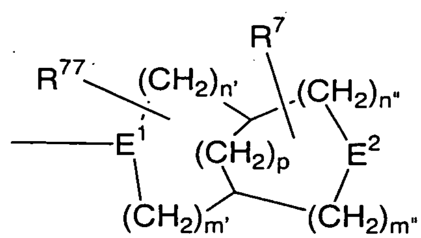


;

A is CH;

B is $-C_{0-3}alkyl-O-C_{0-3}alkyl-$;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}alkyl)$;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, $C_{1-6}alkyl-$ group, $C_{2-6}alkenyl-$ group, $C_{4-6}cycloalkyl-C_{0-6}alkyl-$ group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-C_{1-4}alkyl-N(C_{0-4}alkyl)-$ group, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, $C_{1-3}alkyl-CO-C_{0-4}alkyl-$ group, $C_{0-6}alkyl-O-C(O)-C_{0-4}alkyl-$ group, $C_{0-6}alkyl-C(O)-O-C_{0-4}alkyl-$ group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)-(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)-$ group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $C_{1-4}alkyl$, $C_{1-6}alkoxyl$, $C_{1-6}alkyl-CO-C_{0-4}alkyl-$, pyrrolidinyl–$C_{0-4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0-4}alkyl$, $-C(O)-O(C_{0-4}alkyl)$, or $-C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

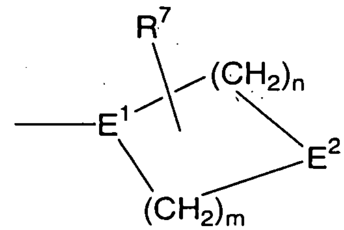
R^{88} and R^8 each is independently –CN, $-C_{0-4}alkyl$, $-C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C(O)-O-C_{0-4}alkyl$ or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is $-C_{0-4}alkyl$, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

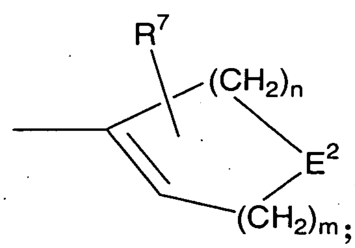
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is CH;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, $C_{1-6}alkyl$– group, $C_{2-6}alkenyl$– group, $C_{4-6}cycloalkyl$-$C_{0-6}alkyl$– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}alkyl$–$N(C_{0-4}alkyl)$– group, –$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, $C_{1-3}alkyl$–CO–$C_{0-4}alkyl$– group, $C_{0-6}alkyl$–O–C(O)–$C_{0-4}alkyl$– group, $C_{0-6}alkyl$–C(O)–O–$C_{0-4}alkyl$– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}alkyl$– group, pyridyl–$C_{0-4}alkyl$– group, pyrimidinyl–$C_{0-4}alkyl$– group, pyrazinyl–$C_{0-4}alkyl$– group, thiophenyl–$C_{0-4}alkyl$– group, pyrazolyl–$C_{0-4}alkyl$– group, imidazolyl–$C_{0-4}alkyl$– group, triazolyl–$C_{0-4}alkyl$– group, azetidinyl–$C_{0-4}alkyl$– group, pyrrolidinyl–$C_{0-4}alkyl$– group, isoquinolinyl–$C_{0-4}alkyl$– group, indanyl–$C_{0-4}alkyl$– group, benzothiazolyl–$C_{0-4}alkyl$– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –$N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $C_{1-4}alkyl$, $C_{1-6}alkoxyl$, $C_{1-6}alkyl$–CO–$C_{0-4}alkyl$–, pyrrolidinyl–$C_{0-4}alkyl$–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0-4}alkyl$, –C(O)-$O(C_{0-4}alkyl)$, or –C(O)-$N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

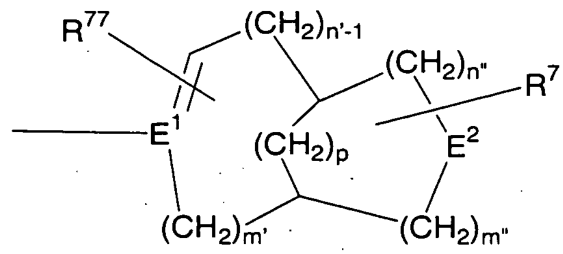
R^{88} and R^8 each is independently –CN, –$C_{0-4}alkyl$, –C(O)-$N(C_{0-4}alkyl)(C_{0-4}alkyl)$, –C(O)-O-$C_{0-4}alkyl$ or 1,3-dioxolan-2-yl–$C_{0-4}alkyl$–;

R^9 is –$C_{0-4}alkyl$, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

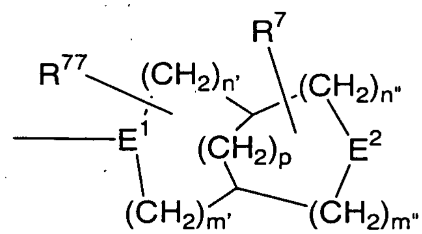
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–

CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

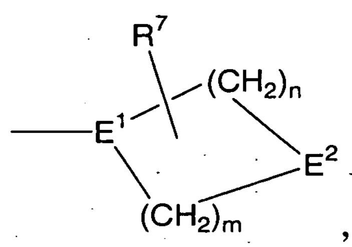
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In a sixth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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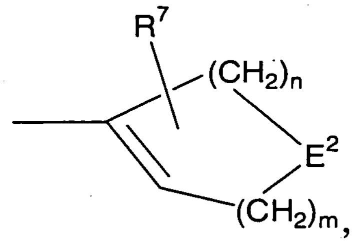
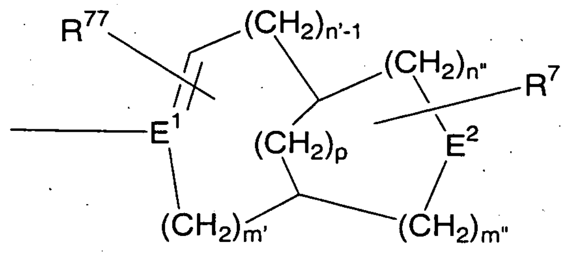
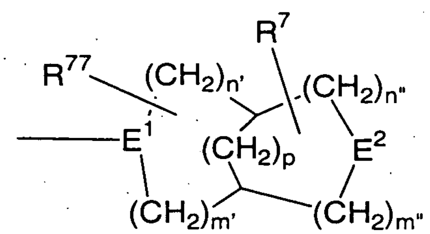




, or



A is CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N;

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-}

4alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

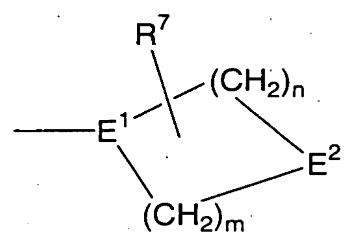
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the sixth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is $-C_{1-6}$alkyl$-$, $-C_{0-3}$alkyl$-$O$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-C_{3-7}$cycloalkyl$-$, $-C_{0-3}$alkyl$-$N(C_{0-3}alkyl)$-$C(O)$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$S$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$PH$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$C(O)$-C_{0-3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form $-$CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-$S(O)$-$, or $-S(O)_2-$;

G^1 is N;

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl$-$ group, C_{2-6}alkenyl$-$ group, C_{4-6}cycloalkyl-C_{0-6}alkyl$-$ group, N(C_{0-4}alkyl)(C_{0-4}alkyl)$-C_{1-4}$alkyl$-$N(C_{0-4}alkyl)$-$ group, $-$N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl$-$CO$-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-$O$-$C(O)$-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-$C(O)$-$O$-C_{0-4}$alkyl$-$ group, N(C_{0-4}alkyl)(C_{0-4}alkyl)$-$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$-$ group, phenyl$-C_{0-4}$alkyl$-$ group, pyridyl$-C_{0-4}$alkyl$-$ group, pyrimidinyl$-C_{0-4}$alkyl$-$ group, pyrazinyl$-C_{0-4}$alkyl$-$ group, thiophenyl$-C_{0-4}$alkyl$-$ group, pyrazolyl$-C_{0-4}$alkyl$-$ group, imidazolyl$-C_{0-4}$alkyl$-$ group, triazolyl$-C_{0-4}$alkyl$-$ group, azetidinyl$-C_{0-4}$alkyl$-$ group, pyrrolidinyl$-C_{0-4}$alkyl$-$ group, isoquinolinyl$-C_{0-4}$alkyl$-$ group, indanyl$-C_{0-4}$alkyl$-$ group, benzothiazolyl$-C_{0-4}$alkyl$-$ group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being $-$OH, $-$N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl$-$CO$-C_{0-4}$alkyl$-$, pyrrolidinyl$-C_{0-4}$alkyl$-$, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, $-$C(O)-O(C_{0-4}alkyl), or $-$C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

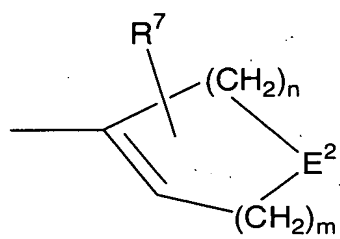
R^{88} and R^8 each is independently $-$CN, $-C_{0-4}$alkyl, $-$C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), $-$C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl$-C_{0-4}$alkyl$-$;

R^9 is $-C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is $-C_{1\text{-}6}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-O-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-NH-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-NH-C_{3\text{-}7}$cycloalkyl$-$, $-C_{0\text{-}3}$alkyl$-N(C_{0\text{-}3}$alkyl$)-C(O)-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-NH-SO_2-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-S-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-SO_2-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-PH-C_{0\text{-}3}$alkyl$-$, $-C_{0\text{-}3}$alkyl$-C(O)-C_{0\text{-}3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH{=}C{<}$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N;

G^2 is N, CH, or $C(C_{1\text{-}3}$alkyl$)$;

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl$-$ group, $C_{2\text{-}6}$alkenyl$-$ group, $C_{4\text{-}6}$cycloalkyl$-C_{0\text{-}6}$alkyl$-$ group, $N(C_{0\text{-}4}$alkyl$)(C_{0\text{-}4}$alkyl$)-C_{1\text{-}4}$alkyl$-N(C_{0\text{-}4}$alkyl$)-$ group, $-N(C_{0\text{-}4}$alkyl$)(C_{0\text{-}4}$alkyl$)$ group, $C_{1\text{-}3}$alkyl$-CO-C_{0\text{-}4}$alkyl$-$ group, $C_{0\text{-}6}$alkyl$-O-C(O)-C_{0\text{-}4}$alkyl$-$ group, $C_{0\text{-}6}$alkyl$-C(O)-O-C_{0\text{-}4}$alkyl$-$ group, $N(C_{0\text{-}4}$alkyl$)(C_{0\text{-}4}$alkyl$)-(C_{0\text{-}4}$alkyl$)C(O)(C_{0\text{-}4}$alkyl$)-$ group, phenyl$-C_{0\text{-}4}$alkyl$-$ group, pyridyl$-C_{0\text{-}4}$alkyl$-$ group, pyrimidinyl$-C_{0\text{-}4}$alkyl$-$ group, pyrazinyl$-C_{0\text{-}4}$alkyl$-$ group, thiophenyl$-C_{0\text{-}4}$alkyl$-$ group, pyrazolyl$-C_{0\text{-}4}$alkyl$-$ group, imidazolyl$-C_{0\text{-}4}$alkyl$-$ group, triazolyl$-C_{0\text{-}4}$alkyl$-$ group, azetidinyl$-C_{0\text{-}4}$alkyl$-$ group, pyrrolidinyl$-C_{0\text{-}4}$alkyl$-$ group, isoquinolinyl$-C_{0\text{-}4}$alkyl$-$ group, indanyl$-C_{0\text{-}4}$alkyl$-$ group, benzothiazolyl$-C_{0\text{-}4}$alkyl$-$ group, any of the groups optionally substituted

with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

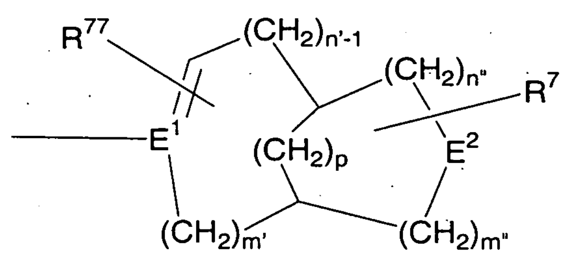
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N;

G^2 is N, CH, or $C(C_{1-3}alkyl)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$C_{1-4}$alkyl–$N(C_{0-4}alkyl)$– group, –$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, $N(C_{0-4}alkyl)(C_{0-4}alkyl)$–$(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)$– group, phenyl–$C_{0-4}$alkyl– group, pyridyl–$C_{0-4}$alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –$N(C_{0-4}alkyl)(C_{0-4}alkyl)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

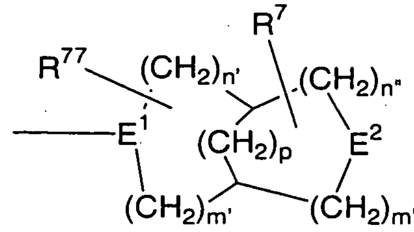
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In yet another embodiment of the fifth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



A is CH;

B is $-C_{1-6}$alkyl$-$, $-C_{0-3}$alkyl$-O-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{3-7}$cycloalkyl$-$, $-C_{0-3}$alkyl$-N(C_{0-3}$alkyl$)-C(O)-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-S-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-PH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-C(O)-C_{0-3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N;

G^2 is N, CH, or $C(C_{1-3}$alkyl$)$;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl$-$ group, C_{2-6}alkenyl$-$ group, C_{4-6}cycloalkyl$-C_{0-6}$alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-C_{1-4}$alkyl$-N(C_{0-4}$alkyl$)-$ group, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)$ group, C_{1-3}alkyl$-CO-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-O-C(O)-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-C(O)-O-C_{0-4}$alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-(C_{0-4}$alkyl$)C(O)(C_{0-4}$alkyl$)-$ group, phenyl$-C_{0-4}$alkyl$-$ group, pyridyl$-C_{0-4}$alkyl$-$ group, pyrimidinyl$-C_{0-4}$alkyl$-$ group, pyrazinyl$-C_{0-4}$alkyl$-$ group, thiophenyl$-C_{0-4}$alkyl$-$ group, pyrazolyl$-C_{0-4}$alkyl$-$ group, imidazolyl$-C_{0-4}$alkyl$-$ group, triazolyl$-C_{0-4}$alkyl$-$ group, azetidinyl$-C_{0-4}$alkyl$-$ group, pyrrolidinyl$-C_{0-4}$alkyl$-$ group, isoquinolinyl$-C_{0-4}$alkyl$-$ group, indanyl$-C_{0-4}$alkyl$-$ group, benzothiazolyl$-C_{0-4}$alkyl$-$ group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being $-OH$, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)$, C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl$-CO-C_{0-4}$alkyl$-$, pyrrolidinyl$-C_{0-4}$alkyl$-$, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

$n' + n'' = n$;

$m' + m'' = m$;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

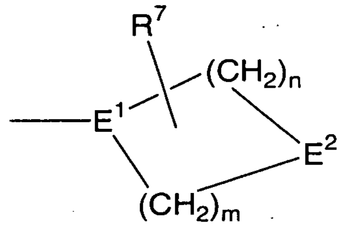
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In a seventh aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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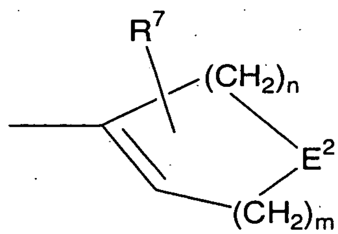

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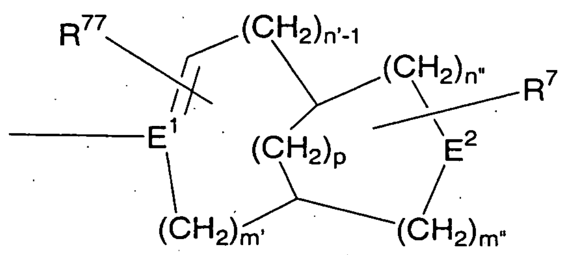
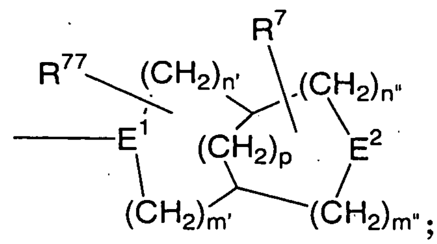


, or



A is CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $-S(O)_2-$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

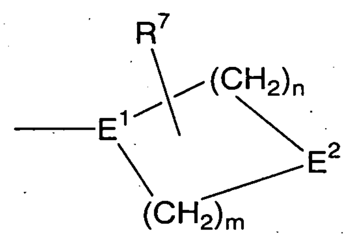
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the seventh aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is –$C_{1\text{-}6}$alkyl–, –$C_{0\text{-}3}$alkyl–O–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{3\text{-}7}$cycloalkyl–, –$C_{0\text{-}3}$alkyl–N($C_{0\text{-}3}$alkyl)–C(O)–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–S–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl– group, $C_{2\text{-}6}$alkenyl– group, $C_{4\text{-}6}$cycloalkyl-$C_{0\text{-}6}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–$C_{1\text{-}4}$alkyl–N($C_{0\text{-}4}$alkyl)– group, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl) group, $C_{1\text{-}3}$alkyl–CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–

$C(O)–O–C_{0\text{-}4}alkyl–$ group, $N(C_{0\text{-}4}alkyl)(C_{0\text{-}4}alkyl)–(C_{0\text{-}4}alkyl)C(O)(C_{0\text{-}4}alkyl)–$ group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, $–N(C_{0\text{-}4}alkyl)(C_{0\text{-}4}alkyl)$, $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –$C(O)$-$O(C_{0\text{-}4}alkyl)$, or –$C(O)$-$N(C_{0\text{-}4}alkyl)(C_{0\text{-}4}alkyl)$;

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

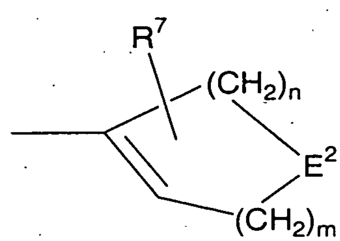
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –$C(O)$-$N(C_{0\text{-}4}alkyl)(C_{0\text{-}4}alkyl)$, –$C(O)$-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an embodiment of the seventh aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is $-C_{1-6}$alkyl$-$, $-C_{0-3}$alkyl$-O-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-C_{3-7}$cycloalkyl$-$, $-C_{0-3}$alkyl$-N(C_{0-3}$alkyl$)-C(O)-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-NH-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-S-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-PH-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-C(O)-C_{0-3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form $-CH=C<$;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, $-S(O)-$, or $-S(O)_2-$;

G^1 is N, CH, or $C(C_{1-3}$alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl$-$ group, C_{2-6}alkenyl$-$ group, C_{4-6}cycloalkyl-C_{0-6}alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-C_{1-4}$alkyl$-N(C_{0-4}$alkyl$)-$ group, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl) group, C_{1-3}alkyl$-CO-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-O-C(O)-C_{0-4}$alkyl$-$ group, C_{0-6}alkyl$-C(O)-O-C_{0-4}$alkyl$-$ group, $N(C_{0-4}$alkyl$)(C_{0-4}$alkyl$)-(C_{0-4}$alkyl$)C(O)(C_{0-4}$alkyl$)-$ group, phenyl$-C_{0-4}$alkyl$-$ group, pyridyl$-C_{0-4}$alkyl$-$ group, pyrimidinyl$-C_{0-4}$alkyl$-$ group, pyrazinyl$-C_{0-4}$alkyl$-$ group, thiophenyl$-C_{0-4}$alkyl$-$ group, pyrazolyl$-C_{0-4}$alkyl$-$ group, imidazolyl$-C_{0-4}$alkyl$-$ group, triazolyl$-C_{0-4}$alkyl$-$ group, azetidinyl$-C_{0-4}$alkyl$-$ group, pyrrolidinyl$-C_{0-4}$alkyl$-$ group, isoquinolinyl$-C_{0-4}$alkyl$-$ group, indanyl$-C_{0-4}$alkyl$-$ group, benzothiazolyl$-C_{0-4}$alkyl$-$ group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being $-OH$, $-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl$-CO-C_{0-4}$alkyl$-$, pyrrolidinyl$-C_{0-4}$alkyl$-$, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, $-C(O)-O(C_{0-4}$alkyl), or $-C(O)-N(C_{0-4}$alkyl$)(C_{0-4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

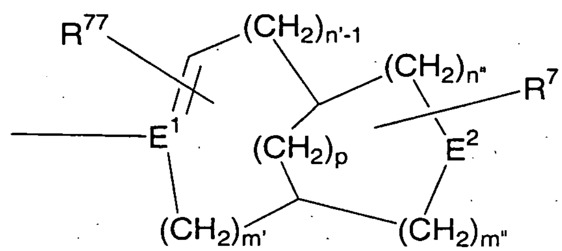
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In another embodiment of the seventh aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is –$C_{1\text{-}6}$alkyl–, –$C_{0\text{-}3}$alkyl–O–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–$C_{3\text{-}7}$cycloalkyl–, –$C_{0\text{-}3}$alkyl–N($C_{0\text{-}3}$alkyl)–C(O)–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–NH–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–S–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl– group, $C_{2\text{-}6}$alkenyl– group, $C_{4\text{-}6}$cycloalkyl-$C_{0\text{-}6}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–$C_{1\text{-}4}$alkyl–N($C_{0\text{-}4}$alkyl)– group, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl) group, $C_{1\text{-}3}$alkyl–CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}$

4alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

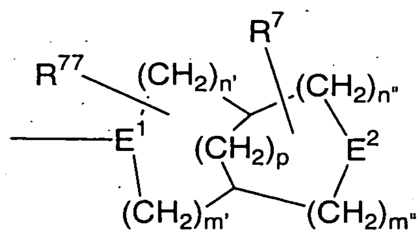
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In still another embodiment of the seventh aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



;

A is CH;

B is –C_{1-6}alkyl–, –C_{0-3}alkyl–O–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–, –C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, –C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–, –C_{0-3}alkyl–S–

$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl– group, $C_{2\text{-}6}$alkenyl– group, $C_{4\text{-}6}$cycloalkyl-$C_{0\text{-}6}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–$C_{1\text{-}4}$alkyl–N($C_{0\text{-}4}$alkyl)– group, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl) group, $C_{1\text{-}3}$alkyl–CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

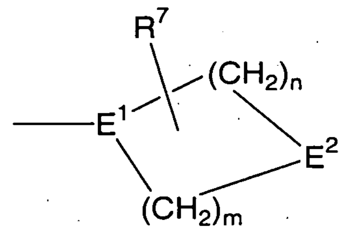
R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In an eighth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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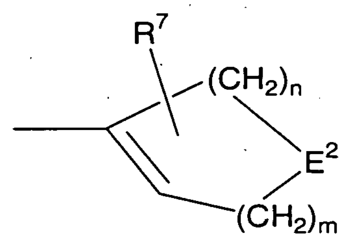

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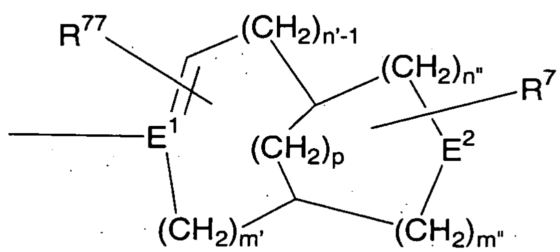

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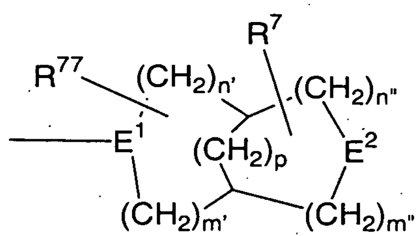


;

A is CH;

B is $-C_{1-6}$alkyl$-$, $-C_{0-3}$alkyl$-$O$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-C_{3-7}$cycloalkyl$-$, $-C_{0-3}$alkyl$-$N(C_{0-3}alkyl)$-$C(O)$-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$NH$-SO_2-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$, $-C_{0-3}$alkyl$-$S$-$

C_{0-3}alkyl–, –C_{0-3}alkyl–SO_2–C_{0-3}alkyl–, –C_{0-3}alkyl–PH–C_{0-3}alkyl–, –C_{0-3}alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH, and A and D are bridged by -C_{1-4}alkyl- to form a fused bicyclo ring with A and D at the bicyclo cusps;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

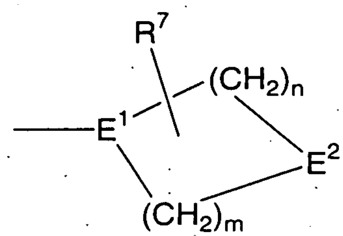
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;

R^9 is –C_{0-4}alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

In a ninth aspect, the present invention provides a compound described by the chemical formula (I), or a pharmaceutically acceptable salt thereof, wherein

Non-Ar-Cyc is



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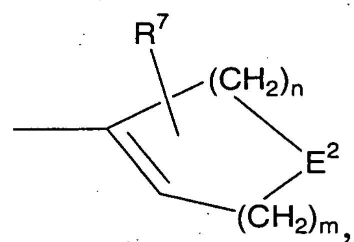

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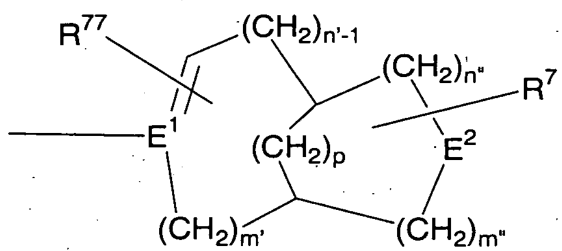

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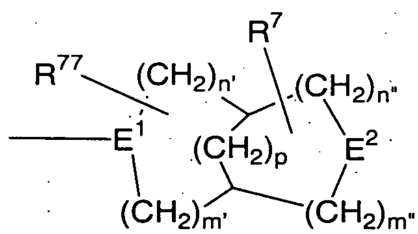


;

A is CH_2;

B is $–C_{1-6}alkyl–$, $–C_{0-3}alkyl–O–C_{0-3}alkyl–$, $–C_{0-3}alkyl–NH–C_{0-3}alkyl–$, $–C_{0-3}alkyl–NH–C_{3-7}cycloalkyl–$, $–C_{0-3}alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–$, $–C_{0-3}alkyl–NH–SO_2–C_{0-3}alkyl–$, $–C_{0-3}alkyl–$, $–C_{0-3}alkyl–S–$

$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–SO_2–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–PH–$C_{0\text{-}3}$alkyl–, –$C_{0\text{-}3}$alkyl–C(O)–$C_{0\text{-}3}$alkyl, or a direct bond;

D is CH_2;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or –$S(O)_2$–;

G^1 is N, CH, or C($C_{1\text{-}3}$alkyl);

G^2 is N;

R, R^7 and R^{77} each independently is hydrogen, $C_{1\text{-}6}$alkyl– group, $C_{2\text{-}6}$alkenyl– group, $C_{4\text{-}6}$cycloalkyl-$C_{0\text{-}6}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–$C_{1\text{-}4}$alkyl–N($C_{0\text{-}4}$alkyl)– group, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl) group, $C_{1\text{-}3}$alkyl–CO–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–O–C(O)–$C_{0\text{-}4}$alkyl– group, $C_{0\text{-}6}$alkyl–C(O)–O–$C_{0\text{-}4}$alkyl– group, N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl)–($C_{0\text{-}4}$alkyl)C(O)($C_{0\text{-}4}$alkyl)– group, phenyl–$C_{0\text{-}4}$alkyl– group, pyridyl–$C_{0\text{-}4}$alkyl– group, pyrimidinyl–$C_{0\text{-}4}$alkyl– group, pyrazinyl–$C_{0\text{-}4}$alkyl– group, thiophenyl–$C_{0\text{-}4}$alkyl– group, pyrazolyl–$C_{0\text{-}4}$alkyl– group, imidazolyl–$C_{0\text{-}4}$alkyl– group, triazolyl–$C_{0\text{-}4}$alkyl– group, azetidinyl–$C_{0\text{-}4}$alkyl– group, pyrrolidinyl–$C_{0\text{-}4}$alkyl– group, isoquinolinyl–$C_{0\text{-}4}$alkyl– group, indanyl–$C_{0\text{-}4}$alkyl– group, benzothiazolyl–$C_{0\text{-}4}$alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), $C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxyl, $C_{1\text{-}6}$alkyl–CO–$C_{0\text{-}4}$alkyl–, pyrrolidinyl–$C_{0\text{-}4}$alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n+m is 2, 3, 4, 5, or 6;

p is 0, 1, 2, or 3;

R^1, R^2, R^3, R^4, and R^6 are each independently halogen, $C_{0\text{-}4}$alkyl, –C(O)-O($C_{0\text{-}4}$alkyl), or –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl);

R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;

R^{88} and R^8 each is independently –CN, –$C_{0\text{-}4}$alkyl, –C(O)-N($C_{0\text{-}4}$alkyl)($C_{0\text{-}4}$alkyl), –C(O)-O-$C_{0\text{-}4}$alkyl or 1,3-dioxolan-2-yl–$C_{0\text{-}4}$alkyl–;

R^9 is –$C_{0\text{-}4}$alkyl, or absent; and

any alkyl optionally substituted with 1-6 independent halogen or -OH.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "aryl" means an aromatic substituent which is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The preferred aryl substituents are phenyl and naphthyl groups.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected by a short C_{1-2}alkyl length to the oxy connecting atom.

The term "C_{0-6}alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC_5alkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls

include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC_{0-4}alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an example, a heteroC_{0-4}alkyl having no carbon atoms but one N atom would be a -NH– if a bridging group and a $-NH_2$ if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines substituted with C_{0-6}alkyl.

The term "carbonyl" unless specifically stated otherwise includes a C_{0-6}alkyl substituent group when the carbonyl is terminal. That is, "carbonyl" means -C(O)-C_{0-6}alkyl unless otherwise stated.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. When a group has an optional substituent, that optional substituent can be on any of the sites readily determined and understood by chemists. That is, for example, a substituent on a cyclopropylC_{1-4}alkyl group can be on the cyclopropyl or on the C_{1-4}alkyl. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the aryl and the aryl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further,

mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

Unless specifically stated otherwise or indicated by a bond symbol (dash or double dash), the connecting point to a recited group will be on the right-most stated group. That is, for example, a phenylalkyl group is connected to the main structure through the alkyl and the phenyl is a substituent on the alkyl.

The compounds of the present invention are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

The pharmaceutically acceptable salts of the compounds of formula I include conventional non-toxic salts or quarternary ammonium salts of the compounds of formula I formed e.g. from non-toxic inorganic or organic acids. For example, non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers. All such isomers, including optical isomers, being included in the present invention.

The invention described herein also includes a pharmaceutical composition which is comprised of a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drugs ("NSAID"), and ix) M2/M3 antagonists.

The invention described herein also includes a method of treating arthritis which is comprised of administering to a mammalian patient in need of such treatment a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, in an amount which is effective to treat arthritis. The invention includes methods of treating arthritis by administering to a mamalian patient in need of such treatment a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, in combination or in coadministration with a COX-2 inhibitor.

The invention described herein also includes a method of treating a cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, in an amount which is effective to treat said cytokine mediated disease.

Of particular interest is a method of treating inflammation in a mammalian patient in need of such treatment, which is comprised of administering to said patient an anti-inflammatory effective amount of a compound described by Formula (I), or a pharmaceutically acceptable salt thereof.

Another method which is of particular interest is a method of treating a cytokine mediated disease as described herein wherein the disease is osteoporosis.

Another method which is of particular interest is a method of treating a cytokine mediated disease as described herein wherein the disease is non-osteoporotic bone resorption.

Yet another method which is of particular interest is a method of treating a cytokine mediated disease as described herein wherein the disease is Crohn's disease.

This invention also relates to a method of treating arthritis in a mammal in need such treatment, which comprises administering to said mammal an amount of a compound of formula I which is effective for treating arthritis. Such method includes the treatment of rheumatoid and osteoarthritis.

When administered to a patient for the treatment of athritis, the dosage used can be varied depending upon the type of arthritis, the age and general condition of the patient, the particular compound administered, the presence or level of toxicity or adverse effects experienced with the drug, and other factors. A representative example of a suitable dosage range is from as low as about 0.01mg/kg to as high as about 100mg/kg. However, the dosage administered is generally left to the discretion of the physician.

This invention also relates to a method of inhibiting the action of p38 in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, to inhibit said action of p38, down to normal levels, or in some cases to subnormal levels, so as to ameliorate, prevent or treat the disease state.

The compounds of formula 1 can be used in the prophylactic or therapeutic treatment of disease states in mammals which are exacerbated or caused by excessive or unregulated cytokines, more specifically IL-1, IL-6, IL-8 or TNF.

The compounds of this invention demonstrates efficacy in the assays described below. Efficacy is shown in the assays by results of less than 10μM. Advantageously, compounds have results less than 1μM. Even more advantageously, compounds have results less than 0.1μM. Still more advantageously, compounds have results in the assays of less than 0.01μM. Because the compounds of formula I inhibit cytokines, such as IL-1, IL-6, IL-8 and TNF, by inhibiting the action of p38 the compounds are useful for treating diseases in which cytokine presence or activity is implicated, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

The compounds described by Formula (I), or a pharmaceutically acceptable salt thereof, are also useful to treat other disease states mediated by excessive or unregulated TNF production or activity. Such diseases include, but are not limited to sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft v. host rejection, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia

secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, AIDS and other viral infections, such as cytomegalovirus (CMV), influenza virus, and the herpes family of viruses such as Herpes Zoster or Simplex I and II.

The compounds described by Formula (I), or a pharmaceutically acceptable salt thereof, are also useful topically in the treatment of inflammation such as in the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The compounds described by Formula (I), or a pharmaceutically acceptable salt thereof, are also useful in treating diseases characterized by excessive IL-8 activity. These disease states include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

The invention thus includes a method of treating psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis, in a mammal in need of such treatment, which comprises administering to said mammal a compound described by Formula (I), or a pharmaceutically acceptable salt thereof, in an amount which is effective for treating said disease or condition.

When administered to a patient for the treatment of a disease in which a cytokine or cytokines are implicated, the dosage used can be varied depending upon the type of disease, the age and general condition of the patient, the particular compound administered, the presence or level of toxicity or adverse effects experienced with the drug, and other factors. A representative example of a suitable dosage range is from as low as about 0.01mg/kg to as high as about 100mg/kg. However, the dosage administered is generally left to the discretion of the physician.

The methods of treatment are preferably carried out by delivering the compound of formula I parenterally. The term 'parenteral' as used herein includes intravenous, intramuscular, or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The instant invention can also be carried out by delivering the compound of Formula I subcutaneously, intranasally, intrarectally, transdermally or intravaginally.

The compounds of Formula I may also be administered by inhalation. By 'inhalation' is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by convention techniques.

The invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I may also be included in pharmaceutical compositions in combination with a second therapeutically active compound.

The pharmaceutical carrier employed may be, for example, either a solid, liquid or gas. Exemples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemples of liquid carriers are syrup, peanut oil, olive oil, water and the like. Examples of gaseous carriers include carbon dioxide and nitrogen.

Similarly, the carrier or diluent may include time delay material well known in the art, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical dosage forms can be employed. If a solid dosage is used for oral administration, the preparation can be in the form of a tablet, hard gelatin capsule, troche or lozenge. The amount of solid carrier will vary widely, but generally will be from about 0.025mg to about 1g. When a liquid dosage form is desired for oral administration, the preparation is typically in the form of a syrup, emulsion, soft gelatin capsule, suspension or solution. When a parenteral dosage form is to be employed, the drug may be in solid or liquid form, and may be formulated for administration directly or may be suitable for reconstitution.

Topical dosage forms are also included. Examples of topical dosage forms are solids, liquids and semi-solids. Solids would include dusting powders, poultices and the like. Liquids include solutions, suspensions and emulsions. Semi-solids include creams, ointments, gels and the like.

The amount of a compound of formula I used topically will, of course, vary with the compound chosen, the nature and severity of the condition, and can be varied in accordance with the discretion of the physician. A representative, topical, dose of a compound of formula I is from as low as about 0.01mg to as high as about 2.0g, administered one to four, preferably one to two times daily.

The active ingredient may comprise, for topical administration, from about 0.001% to about 10% w/w.

Drops according to the present invention may comprise sterile or non-sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container aseptically. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous liquid, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

ASSAYS

Protein expression and purification.

Murine p38 containing the FLAG epitope tag was expressed in Drosophila S2 cells under transcriptional control of a copper-inducible

metallothionein promoter. Expression of recombinant p38 was induced by treating transfected cells with 1mM $CuSO_4$ for 4 hours. To generate active recombinant murine p38, $CuSO_4$-treated S2 cells were stimulated 10 minutes prior to harvest with 400mM NaCl, 2mM Na_3VO_4, and 100μg/L okadaic acid. Cell pellets were washed with phosphate-buffered saline, 2mM Na_3VO_4, and lysed in 20mM Tris HCl, pH 7.5, 120mM NaCl, 1% Triton X-100, 2mM EDTA, 20mM NaF, 4mM Na_3VO_4, 2mM Prefabloc SC (Boehringer Mannheim). Cell lysates were centrifuged for 10min at 13,000 x g, and activated, recombinant murine p38 was immunoaffinity purified from the lysate by column chromatography through anti-FLAG M2 resin (Kodak) that had been equilibrated with lysis buffer. After loading the extract the resin was washed with 10 column volumes of lysis buffer, 10 column volumes buffer A (10mM Tris HCl, pH 7.5, 500mM NaCl, 20% glycerol) and 10 column volumes of buffer B (10mM Tris HCl pH 7.5, 150mM NaCl, 20% glycerol). The fusion protein was eluted in buffer B containing 100μg/mL FLAG peptide (Kodak).

The N-terminal 115 amino acids of ATF-2 was expressed in E. coli as a fusion protein with glutathione-S-transferase. The fusion protein was purified over glutathione agarose according to standard procedures (Pharmacia).

p38 kinase assay.

p38 kinase assays were performed in a reaction volume of 100μL in a 96-well plate, at 30° for 45-1200min under the following conditions: 25mM Hepes, pH 7.4, 10mM$MgCl_2$, 20mM β-glycerolphosphate, 2mM DTT, 5μM ATP, 10μCi [γ-^{33}P]-ATP and ~ 2 μM GST-ATF2. Serial dilutions of compounds were added to each reaction in 2μL DMSO. 2μL of DMSO was added to the last row of each reaction plate as the no inhibitor control for each inhibitor titration. The reaction was terminated with an equal volume of a stop solution containing 100mM EDTA and 15mM sodium pyrophosphate. PVDF filter plates (MAIPNOB50, Millipore) were pre-wet with methanol and washed with the stop solution. 50μL aliquots from a single reaction were applied to the filter under vacuum, and the filter was washed twice with 75mM phosphoric acid. The filter plates were counted in a scintillation counter (Top Count, Packard) and the percent inhibition at each compound concentration is determined.

TNF-α release assay.

Blood was obtained from healthy volunteers by venipuncture using sodium heparin as an anti-coagulant. Peripheral blood mononuclear cells (PBMCs)

were isolated using Lymphocyte Separation Medium (ICN) according to manufacturers specifications. Isolated PBMCs were washed 3 times with HBSS and diluted to a density of 2 x 10^6 cells/mL in RPMI + 5% autologous human serum. 50μL of the serial dilutions of inhibitor were added to wells of a 96-well tissue culture plate followed by addition of 100μL of PBMCs and then 50μL of RPMI complete medium containing 400ng/mL LPS. A control well of cells without compound but with LPS (maximal stimulation control) and one without compound and without LPS (background control) were included in each titration. The cells were incubated for 16 hours in a humidified incubator at 37°C , 5% CO_2. Supernatants were then harvested and TNF-α levels were quantified by immunoassay using commercial reagents (R&D, Inc).

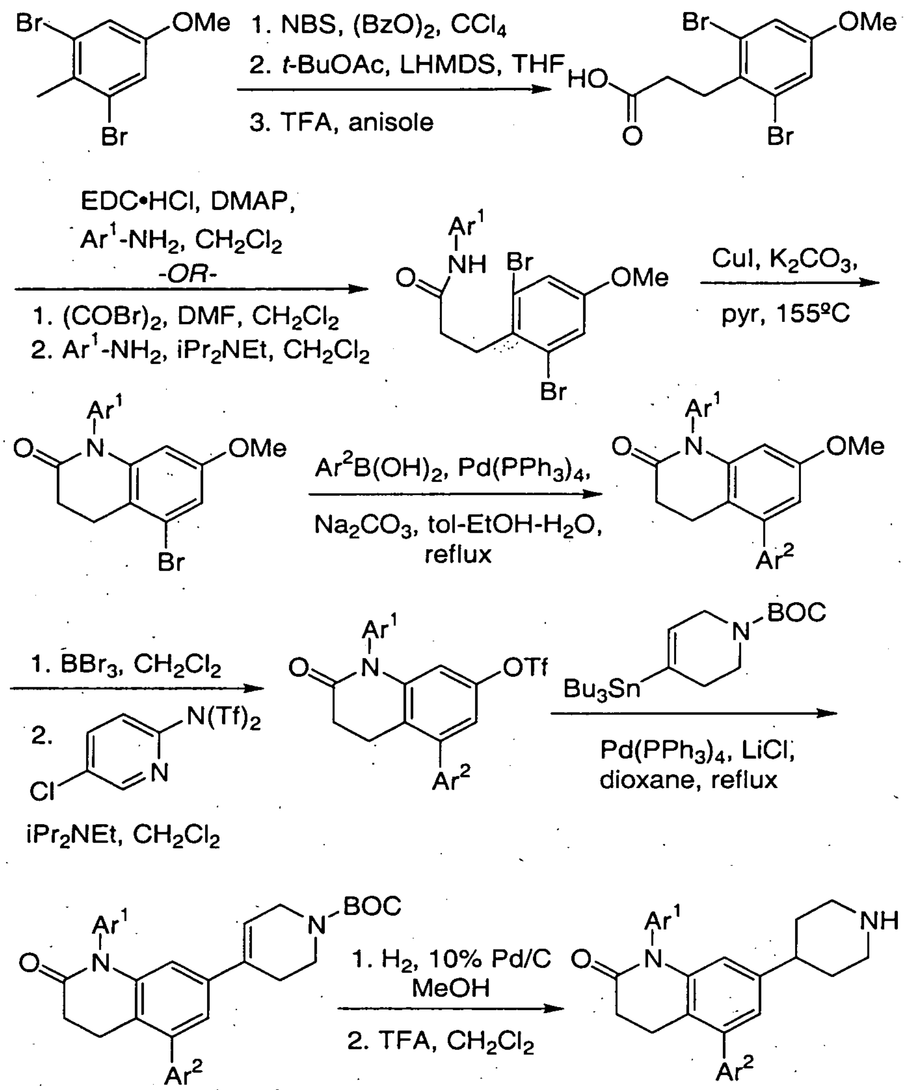
The compounds of this invention demonstrated efficacy in the above assays by results of less than 10μM. Advantageous compounds had results less than 1μM. Even more advantageous compounds had results less than 0.1μM. Still more advantageous compounds had results in the assays of less than 0.01μM.

Compounds described by Formula (IIIA) are less advantageous because such compounds tend to be less stable. Accordingly, such compounds need to be tested for stability and stabilized if appropriate before use.

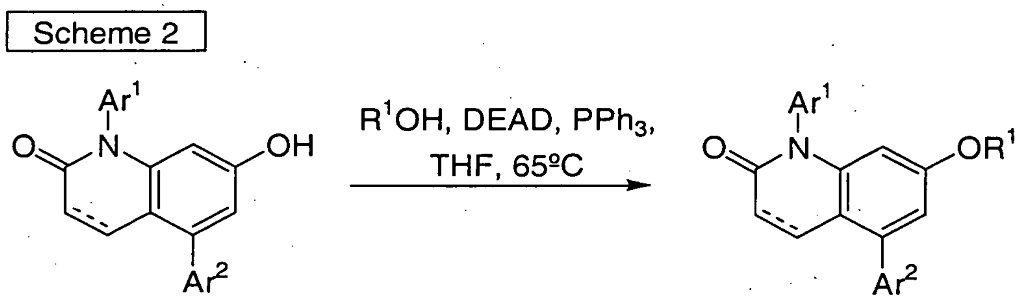
EXAMPLES

The compounds of the present invention are prepared by the following illustrative schemes:

Scheme 1


Br
OMe
Br
1. NBS, $(BzO)_2$, CCl_4
2. t-BuOAc, LHMDS, THF
3. TFA, anisole
HO
O
EDC•HCl, DMAP,
Ar^1-NH_2, CH_2Cl_2
-OR-
1. $(COBr)_2$, DMF, CH_2Cl_2
2. Ar^1-NH_2, iPr_2NEt, CH_2Cl_2
Ar^1
NH
CuI, K_2CO_3,
pyr, 155ºC
N
$Ar^2B(OH)_2$, $Pd(PPh_3)_4$,
Na_2CO_3, tol-EtOH-H_2O,
reflux
Ar^2
1. BBr_3, CH_2Cl_2
2.
$N(Tf)_2$
Cl
iPr_2NEt, CH_2Cl_2
OTf
BOC
Bu_3Sn
$Pd(PPh_3)_4$, LiCl,
dioxane, reflux
1. H_2, 10% Pd/C
MeOH
2. TFA, CH_2Cl_2
NH

Scheme 2:



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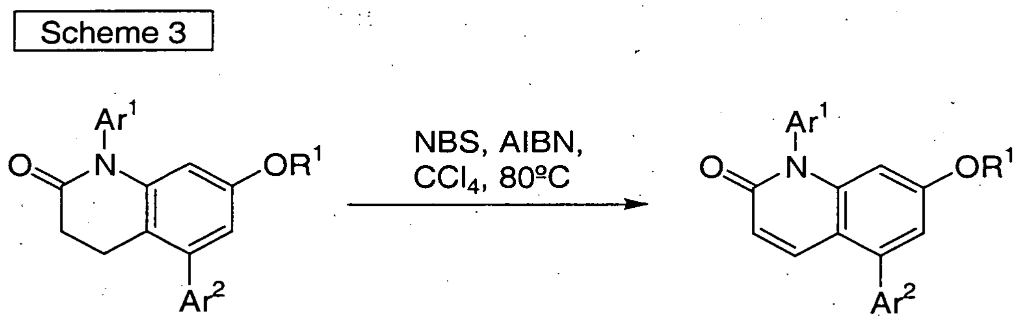

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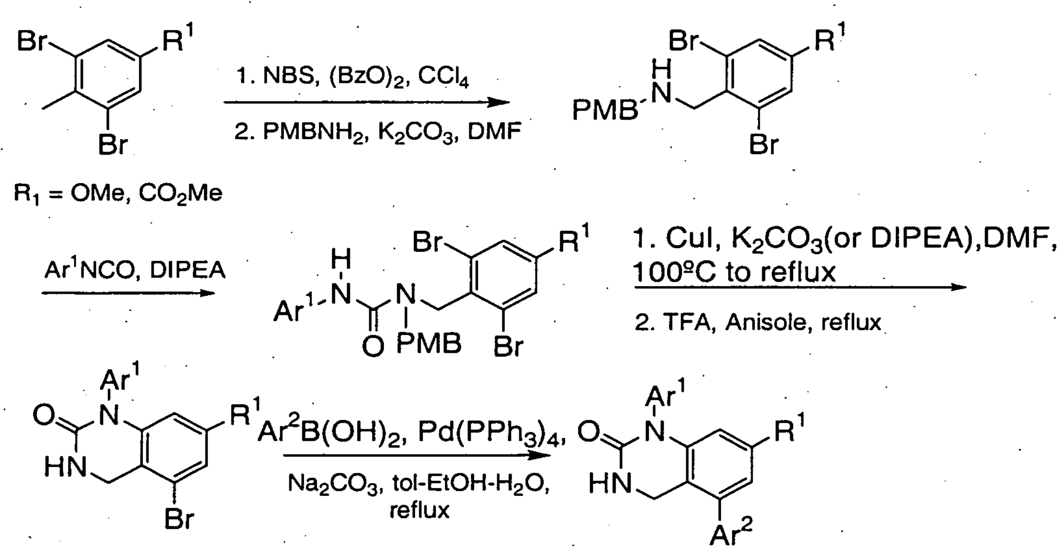

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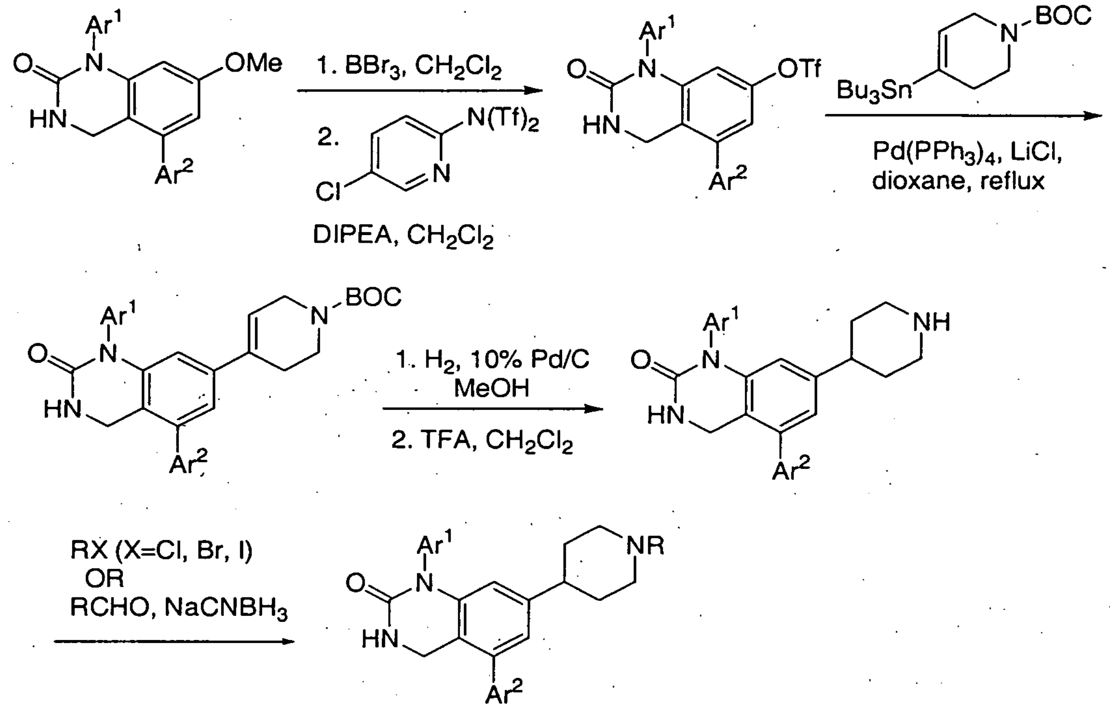

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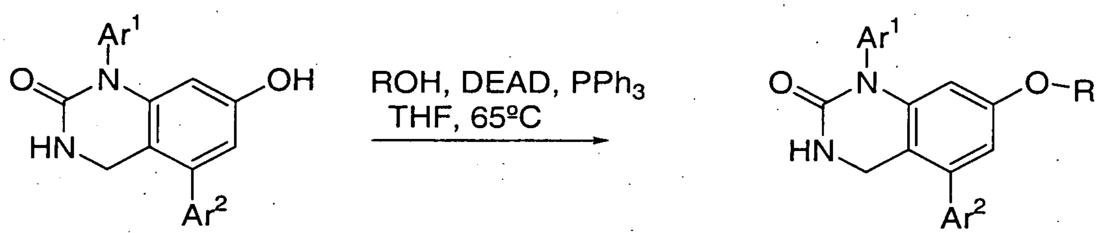
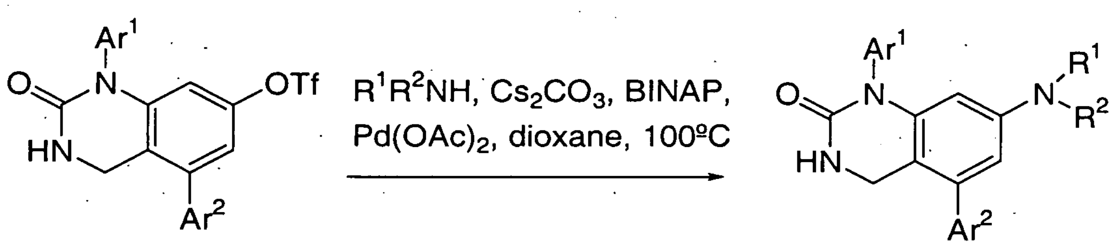
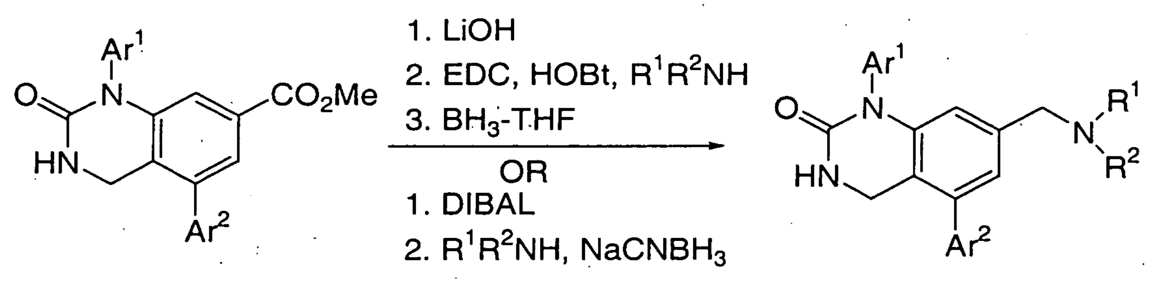


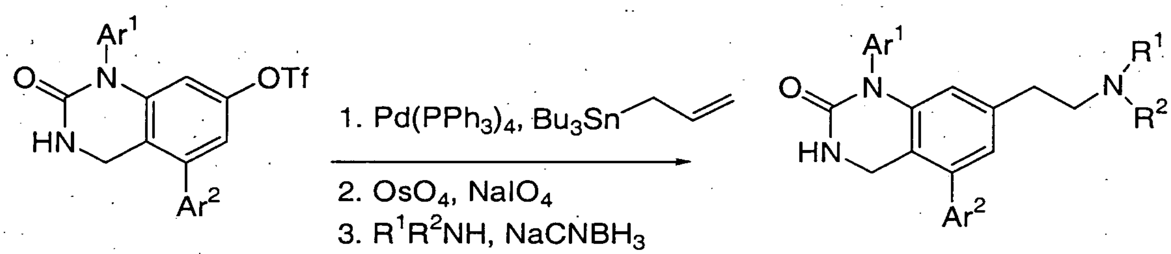
Scheme 7:



Scheme 8:



Scheme 9:



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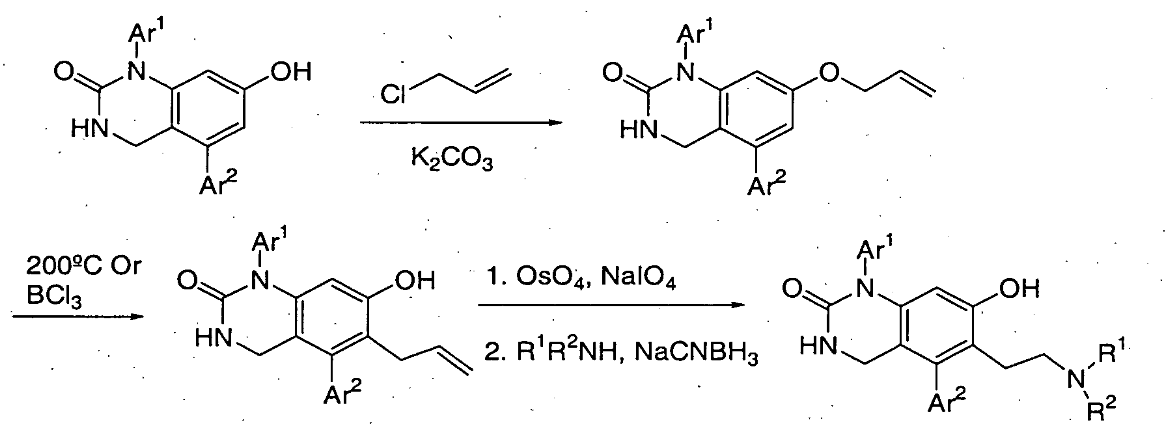
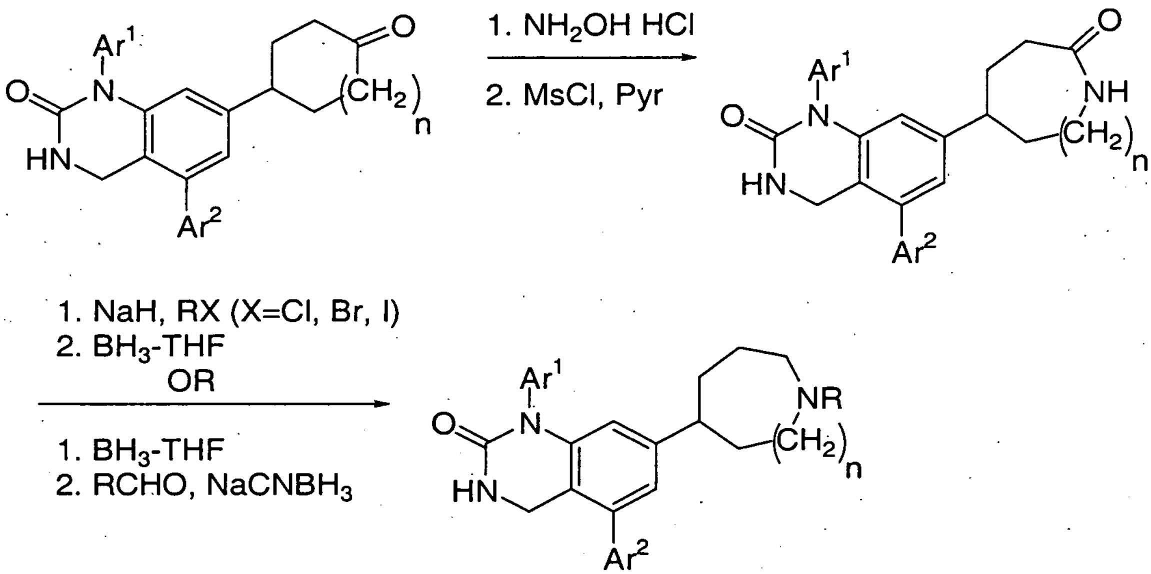


Scheme 11:



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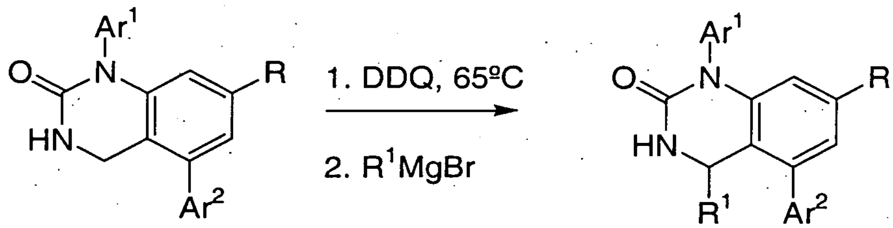
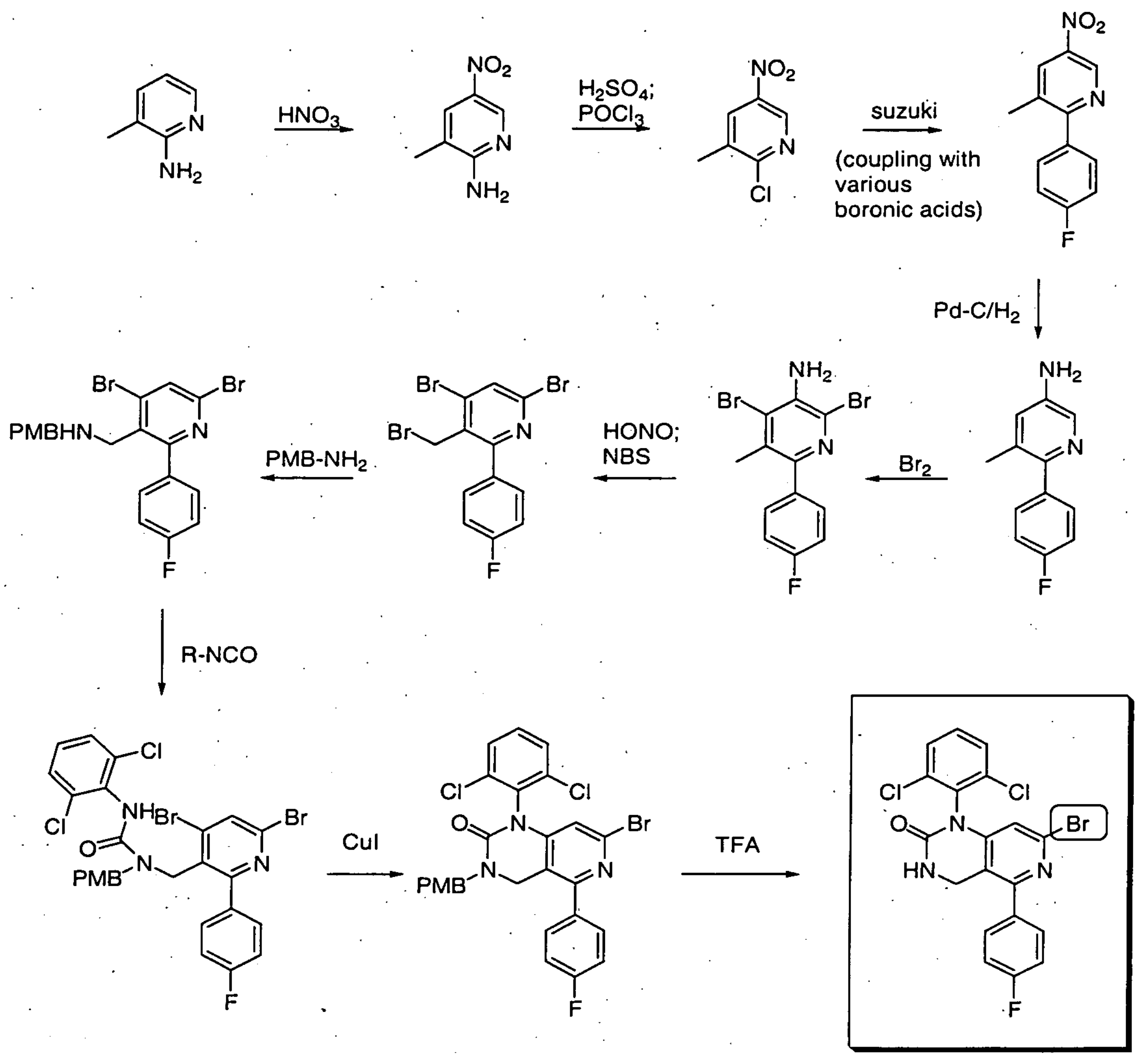
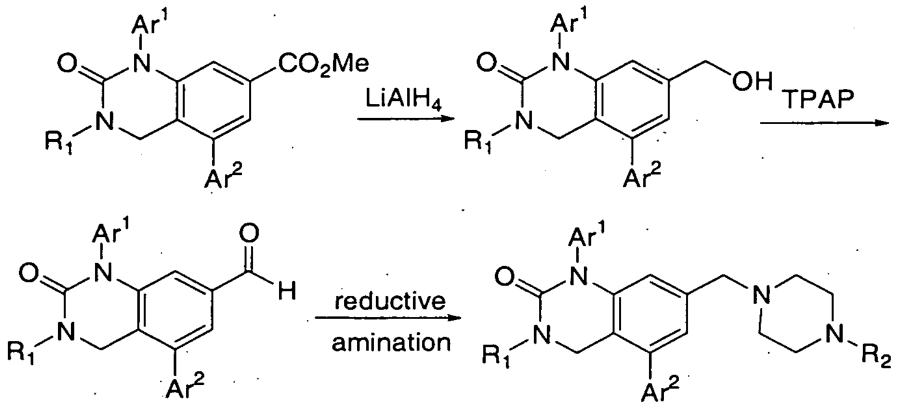


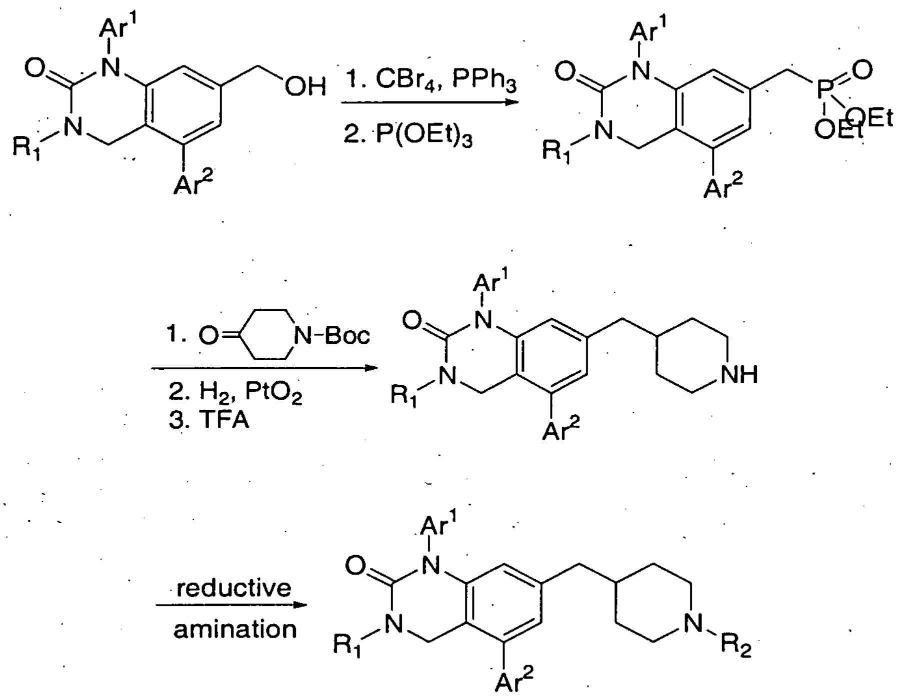
Scheme 13:



Scheme 14:



Scheme 15:



HPLC CONDITIONS

LC 1. Retention time using the following conditions:

Column: YMC ODS A, 5m, 4.6 x 50mm;

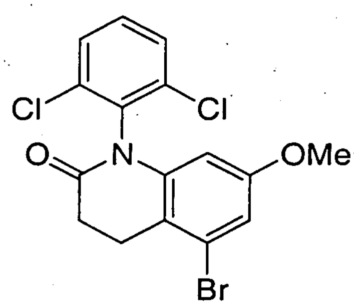
Gradient Eluent: 10:90 to 95:5 v/v acetonitrile/water + 0.05% TFA over 4.5min;

Detection: PDA, 200-600nm; Flow Rate: 2.5mL/min.

LC 2. Retention time using the following conditions:
Column: YMC Pro-C18, 5m, 4.6 x 50mm;
Gradient Eluent: 10:90 to 95:5 v/v acetonitrile/water + 0.05% TFA over 3.0min;
Detection: PDA, 200-600nm; Flow Rate: 2.5mL/min.

INTERMEDIATE 1

5-Bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone



Step A: 2,6-Dibromo-4-methoxy-benzyl bromide

To a suspension of 5.0g of 2,6-dibromo-4-methoxytoluene in 90mL of CCl_4 was added *N*-bromosuccinimide and benzoyl peroxide. The resulting mixture was heated to reflux and stirred at the refluxing temperature while irradiating with a sunlamp for 2h, then cooled and concentrated. The resulting residue was dissolved in 1:1 hexanes-Et_2O and filtered through a pad of silica gel, then purified by flash chromatography on a Biotage 40M column, eluting with 98:2 hexanes-Et_2O, to yield 2,6-Dibromo-4-methoxy-benzyl bromide as a pale yellow solid. ^1H NMR (500MHz, $CDCl_3$): δ 7.11 (s, 2H); 4.82 (s, 2H); 3.80 (s, 3H).

Step B: *t*-Butyl 3-(2,6-dibromo-4-methoxyphenyl)-propionate

To 5mL of THF at -78°C was added 6.5mL of a 1.0M solution of lithium hexamethyldisilazane in THF. *t*-Butyl acetate (0.9mL) was added dropwise to the resulting cold solution, and the resulting mixture was stirred for 10min at -78°C. 2,6-Dibromo-4-methoxy-benzyl bromide (1.2g) in 5mL of CCl_4 was added dropwise over 5min. The mixture was stirred 20min at -78°C, then quenched by addition of 1mL of saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature, diluted with 50mL of saturated aqueous $NaHCO_3$, and extracted with 3 X 20mL of EtOAc. The combined organics were washed with 25mL of brine, dried over $MgSO_4$, and concentrated to yield *t*-Butyl 3-(2,6-dibromo-4-methoxyphenyl)-propionate as an

oily yellow solid. Mass spectrum (ESI) 320.9 (M-OtBu). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.08 (s, 2H); 3.76 (s, 3H); 3.20 (m, 2H); 2.45 (m, 2H); 1.47 (s, 9H).

Step C: 3-(2,6-dibromo-4-methoxyphenyl)-propionic acid

To a solution of *t*-butyl 3-(2,6-dibromo-4-methoxyphenyl)-propionate (1.32g) in 3.6mL of anisole was added 20mL of trifluoroacetic acid dropwise. The resulting mixture was stirred for 20min at room temperature, then concentrated. The resulting residue was redissolved in 20mL of EtOAc and extracted with 40mL of pH 4 buffer solution. The aqueous phase was extracted with 2 X 20mL of EtOAc and the combined resulting organics were washed with 20mL of brine, dried over $MgSO_4$, and concentrated to yield 3-(2,6-dibromo-4-methoxyphenyl)-propionic acid as a pale yellow solid. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.09 (s, 2H); 3.77 (s, 3H); 3.27 (m, 2H); 2.62 (m, 2H).

Step D: *N*-(2,6-Dichlorophenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide

To a –78°C solution of 11.56g of 3-(2,6-dibromo-4-methoxyphenyl)-propionic acid in 300mL of CH_2Cl_2 was added dropwise 17.1mL of a 1.0M solution of oxalyl bromide, then 1.7mL of DMF. The mixture was allowed to warm to room temperature. When gas evolution ceased, the mixture was recooled to –78°C. Diisopropyl ethylamine (7.14mL) was added dropwise, then a solution of 5.54g of 2,6-dichloroaniline in 10mL of CH_2Cl_2 was added dropwise. The mixture was allowed to warm to room temperature, then stirred overnight at this temperature. The white precipitate was collected to yield the *N*-(2,6-Dichlorophenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide as a white solid. The filtrate was concentrated and recrystallized from EtOH to yield an additional amount of *N*-(2,6-Dichlorophenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide as a white solid. Mass spectrum (ESI) 481.9 (M+1). ^{1}H NMR (500MHz, DMSO-d6): δ 9.89 (s, 1H); 7.53 (d, J=8.2 Hz, 2H); 7.34 (t, J=8.0 Hz, 1H); 7.27 (s, 2H); 3.77 (s, 3H); 3.16 (m, 2H); 2.53 (m, 2H).

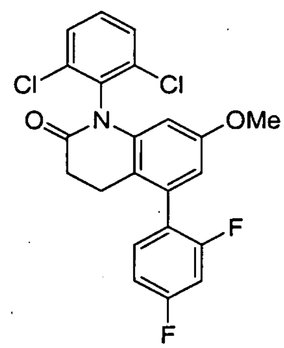
Step E: 5-Bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone

To a suspension of 340mg of *N*-(2,6-dichlorophenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide in 20mL of pyridine was added CuI (137mg) and powdered, dried K_2CO_3 (99mg). The resulting mixture was heated to 160°C in a sealed tube overnight (20h), then concentrated. The reside was purified by flash chromatography on a Biotage 40S column, eluting with 100% CH_2Cl_2, to yield 5-Bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone as a white solid. Mass spectrum (ESI) 402.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.48 (d,

J=8.0 Hz, 2H); 7.34 (t, J=8.0 Hz, 1H); 6.83 (d, J=2.5 Hz, 1H); 5.77 (d, J=2.5 Hz, 1H); 3.67 (s, 3H); 3.18 (m, 2H); 2.84 (m, 2H).

INTERMEDIATE 2

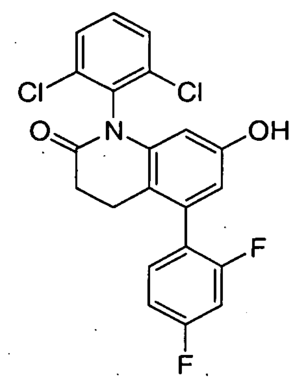
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone



A mixture of 24mg of 5-bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 1**), 28mg of 2,4-difluorophenylboronic acid, 3mg of $Pd(Ph_3P)_4$, and 0.15mL of a 1M aqueous Na_2CO_3 solution in 2mL of toluene and 0.2mL of EtOH in a 10mL flask equipped with a reflux condenser was evacuated and purged three times with Ar. The mixture was heated to reflux and stirred at this temperature for 3.5h, then cooled and diluted with 15mL EtOAc and 10mL of saturated aqueous $NaHCO_3$. The phases were separated and the organic phase was dried over $MgSO_4$ and concentrated. The resulting residue was purified by preparative thin-layer chromatography, eluting with 3:1 hexanes-EtOAc, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone. Mass spectrum (ESI) 434.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.50 (d, J=8.0 Hz, 2H); 7.35 (t, J=8.0 Hz, 1H); 7.32 (m, 1H); 6.96, (m, 2H); 6.52 (d, J=2.5 Hz, 1H); 5.89 (d, J=2.5 Hz, 1H); 3.69 (s, 3H); 2.64-3.00 (m, 4H).

INTERMEDIATE 3

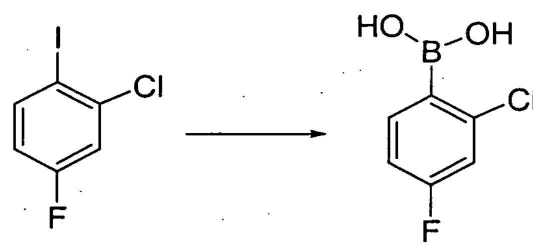
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone



To a solution of 18mg of 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 2**) in 1mL of CH_2Cl_2 was added 0.1mL of BBr_3. The resulting mixture was stirred 30min at 0°C, then warmed to room temperature and stirred at this temperature for 1h. The mixture was concentrated and the resulting residue was purified preparative thin layer chromatography, eluting with 98:2 CH_2Cl_2-MeOH, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone. Mass spectrum (ESI) 421.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.47 (d, J=8.0 Hz, 2H); 7.33 (t, J=8.0 Hz, 1H); 7.27 (m, 1H); 6.95, (m, 2H); 5.82 (s, 1H); 5.23 (s, 1H); 2.56-3.00 (m, 5H).

INTERMEDIATE XI

2-chloro-4-fluoro-phenylboronic acid

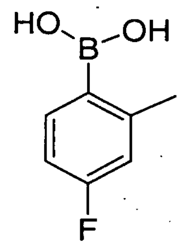


A solution of isopropyl magnesium chloride (100mL, 2.0M in Ethyl Ether) was added to a solution of 2-chloro-4-fluoro-1-iodobenzene (25g, 97.5mmol) in 300mL THF chilled in an ice bath. The solution was then stirred at RT overnight. The solution was chilled in a CO_2/acetone bath and trimethyl borate was added (23mL, 200mmol). The solution was warmed to RT and stirred for 6h. The suspension was partitioned between water and ethyl ether (emulsion). The phases were separated and the organic phase concentrated. The residue was treated with 200mL 2N HCl and stirred overnight. The suspension was then extracted with ethyl

ether (2X) and the combined organics washed with brine, dried over $MgSO_4$, filtered and concentrated to give 13.3g solid. The crude solid was suspended in hexanes, filtered and washed 2X (hexanes) to give 2-chloro-4-fluoro-phenylboronic acid. LC 1: 1.65 min.

INTERMEDIATE XII

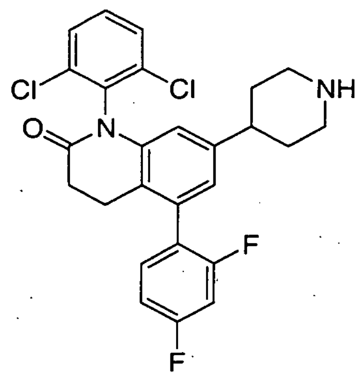
2-methyl-4-fluoro-phenylboronic acid



To dry magnesium (1.13g, 46.4mmol) in 25mL THF was added a small amount of 1,2-dibromoethane (2drops) and iodine (2crystals). 1-Bromo-4-fluoro-2-methylbenzene (4.95mL, 39.15mmol) was added the resulting solution was refluxed for 4h. The solution was cooled to RT and transferred by syringe to a solution of trimethylborate (4.5mL, 40mmol) in 20mL THF at -78°C. The solution was warmed to RT and stirred for 2days. Water (200mL) was added and the mixture was concentrated (to remove most of the organics). The mixture was then treated with 2N HCl (200mL) and stirred 2hrs. The suspension was extracted with ethyl ether, dried over $MgSO_4$, filtered and concentrated to give 2-methyl-4-fluoro-phenylboronic acid. LC 1: 1.72min.

EXAMPLE 1

1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(piperidinyl)-2(1*H*)-quinolinone



Step A: <u>1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone</u>

To a -78°C solution of 24mg of 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 3**) in 1mL of CH_2Cl_2 was added 27mg of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, and 6μL of diisopropylethylamine. The resulting mixture was stirred 30min at -78°C, then warmed to room temperature and stirred at this temperature for 2h. The mixture was concentrated and the resulting residue was purified by preparative thin layer chromatography, eluting with 1:1 hexanes-EtOAc, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone. Mass spectrum (ESI) 552.1 (M+1).

Step B: <u>7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-2(1*H*)-quinolinone</u>

A mixture of 22mg of 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone, 28mg of 1-*tert*-butoxycarbonyl-4-trimethylstannyl-1,2,3,6-tetrahydropyridine (See EXAMPLE 41), 7mg of $Pd(Ph_3P)_4$, and 10mg of crushed, dried LiCl in 1mL of dioxane in a 5mL flask equipped with a reflux condenser was evacuated and purged three times with Ar. The mixture was heated to reflux and stirred at this temperature for 4.5h, filtered through Celite, washing with EtOAc and 10mL of saturated aqueous $NaHCO_3$, then concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 3:1 hexanes-EtOAc, to yield 7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-2(1*H*)-quinolinone. Mass spectrum (ESI) 585.2 (M+1).

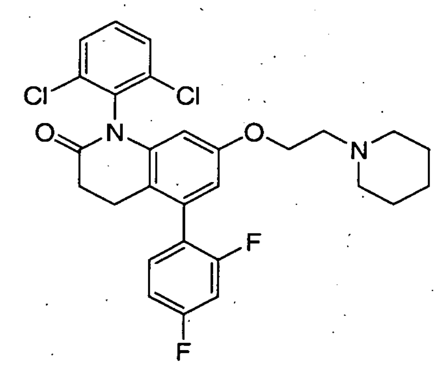
Step C: <u>1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone</u>

A solution of 55mg of 7-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-2(1*H*)-quinolinone and 27mg of 10% palladium on carbon in 12mL of MeOH was hydrogenated in a Parr shaker at 22psi for 45min. The resulting compound was purified by preparative thin-layer chromatography, eluting with 2:1 hexanes-EtOAc, to yield 1-(2,6-dichlorophenyl)-5-(2,5-difluorophenyl)-3,4-dihydro-7-(1-*tert*-butoxycarbonyl-4-piperidinyl)-2(1*H*)-quinolinone.

To a solution of this quinolinone compound (32mg) in 2mL of methylene chloride was added 1mL of trifluoroacetic acid. The resulting mixture was stirred at room temperature for 1h, then diluted with EtOAc, extracted with 2N NaOH saturated with sodium chloride, dried over Na_2SO_4, and purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-MeOH, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone. Mass spectrum (ESI) 488.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.52 (d, J=8.5 Hz, 2H); 7.38 (t, J=8.5 Hz, 1H); 7.29 (br q, J=8.5 Hz, 1H); 6.99 (dt, J=2,5, 8.0 Hz, 1H); 6.94 (dt, J=2,5, 9.0 Hz, 1H); 6.85 (br s, 1H); 6.13 (br s, 1H); 2.19 (br d, J=12 Hz, 2H); 2.90-3.02 (m, 1H); 2.66-3.02 (m, 4H); 2.51 (m, 1H); 1.79 (br d, J=13 Hz, 2H); 1.59 (m, 3H).

EXAMPLE 2

<u>1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-[2-(1-piperidinyl)ethoxy]-2(1*H*)-quinolinone</u>

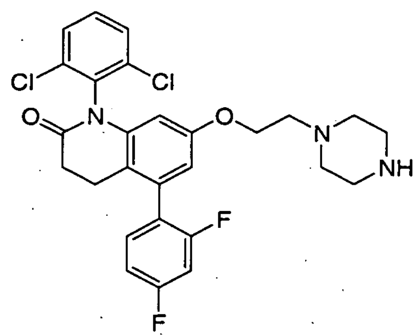


To a solution of 10mg of 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 3**) dissolved in 2mL of anhydrous THF was added 87mg of Ph_3P and 43mg of 1-piperidine ethanol. The resulting mixture was heated to 65°C for 10min. Then 72mg of diisopropyl azodicarboxylate was added dropwise over 2min and the mixture was

stirred for 1h at 65°C. The resulting reaction mixture was concentrated and purified by preparative thin-layer chromatography, eluting with 100% EtOAc, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-[2-(1-piperidinyl)ethoxy]-2(1*H*)-quinolinone. Mass spectrum (ESI) 531.3 (M + 1). ^{1}H NMR (500MHz, $CDCl_3$): δ ^{1}H NMR (500MHz, $CDCl_3$) δ 7.51 (d, J=8 Hz, 2H); 7.38 (t, J=8 Hz, 1H); 7.31 (q, J=6.5 Hz, 1H); 6.98 (m, 2H); 6.54 (s, 1H); 5.90 (s, 1H); 4.08 (s, 2H); 2.83 (m, 6H); 2.61 (s, 4H); 1.68 (s, 4H); 1.48 (s, 2H).

EXAMPLE 3

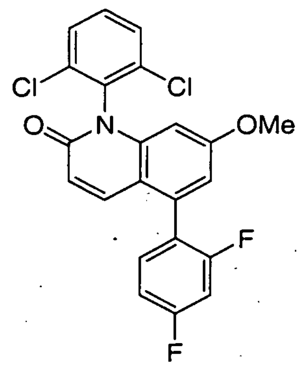
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-[2-(1-piperazinyl)ethoxy]-2(1*H*)-quinolinone



1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-[2-(1-piperazinyl)ethoxy]-2(1*H*)-quinolinone was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 3**) and 1-piperazine ethanol by a procedure analogous to that described in **EXAMPLE 2**. Mass spectrum (ESI) 532.3 (M + 1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.51 (d, J=8.5 Hz, 2H); 7.36 (t, J=8 Hz, 1H); 7.29 (q, J=6 Hz, 1H); 6.96 (m, 2H); 6.52 (s, 1H); 5.90 (s, 1H); 3.96 (t, J=5.5 Hz, 2H); 2.88 (m, 4H); 2.70 (m, 4H); 2.47 (br, 4H); 2.10 (br, 2H).

INTERMEDIATE 4

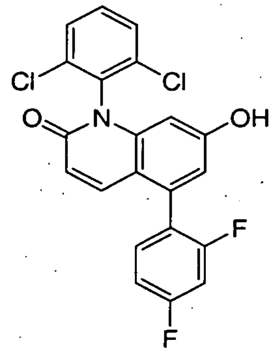
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-methoxy-2(1*H*)-quinolinone



To a solution of 11mg of 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone in 2.5mL of CCl_4 was added 12mg of *N*-bromosuccinimide and 6mg of 2,2'azobis(2-methylpropionitrile). The mixture was heated to 80°C for 1.5h, then concentrated and purified by preparative thin-layer chromatography, eluting with 1:1 hexanes-EtOAc, to yield 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-methoxy-2(1*H*)-quinolinone. Mass spectrum (ESI) 432.1 (M + 1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.56 (m, 3H); 7.44 (m, 1H); 7.37 (m, 1H); 7.02 (m, 2H); 6.76 (s, 1H); 6.58 (d, J=10 Hz, 1H); 6.01 (s, 1H); 3.73 (s, 3H).

INTERMEDIATE 5

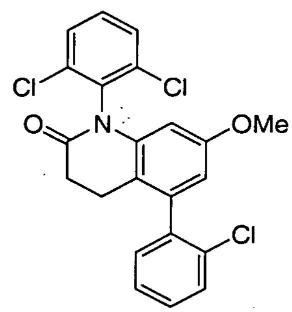
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-hydroxy-2(1*H*)-quinolinone



1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-hydroxy-2(1*H*)-quinolinone was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 4**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 418.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.57 (d, J=8 Hz, 1H); 7.47 (d, J=7.5 Hz, 2H); 7.33 (m, 2H); 7.02 (m, 2H); 6.96 (s, 1H); 6.52 (d, J=9.5, 1H); 6.01 (s, 1H).

INTERMEDIATE 6

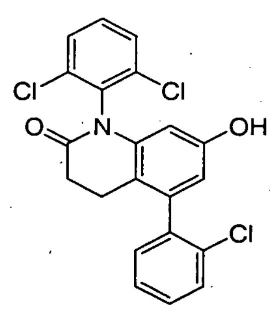
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone was prepared from 5-bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 1**) and 2-chlorophenylboronic acid by a procedure analogous to that described in **INTERMEDIATE 2**. Mass spectrum (ESI) 434.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.44-7.54 (m, 2H); 7.30-7.42 (m, 4H); 6.48 (d, J=2.5 Hz, 1H); 5.89 (d, J=2.5 Hz, 1H); 3.69 (s, 3H); 2.63-2.88 (m, 4H).

INTERMEDIATE 7

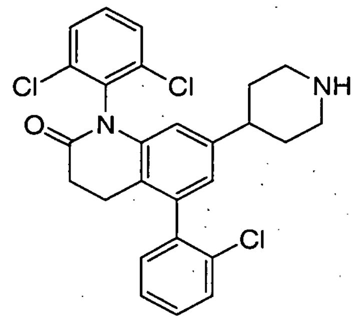
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 6**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 418.1 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.43-7.52 (m, 2H); 7.22-7.40 (m, 4H); 6.38 (d, J=2.5 Hz, 1H); 5.82 (d, J=2.5 Hz, 1H); 2.58-2.85 (m, 4H).

EXAMPLE 4

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(piperidinyl)-2(1*H*)-quinolinone



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone **(INTERMEDIATE 7)** by a procedure analogous to that described in **EXAMPLE 1**, Step A. Mass spectrum (ESI) 550.0 (M+1).

Step B: 7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone

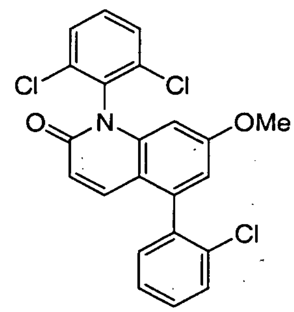
7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step B. Mass spectrum (ESI) 583.2 (M+1).

Step C: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone was prepared from 7-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step C. Mass spectrum (ESI) 485.2 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.52 (m, 3H); 7.36 (m, 4H); 6.82 (s, 1H); 6.15 (s, 1H); 3.12 (d, J=12 Hz, 2H); 2.79 (m, 4H); 2.66 (t, J=12 Hz, 2H); 2.49 (m, 1H); 1.88 (s, 1H); 1.75 (d, J=12.5 Hz, 2H); 1.49 (m, 2H).

INTERMEDIATE 8

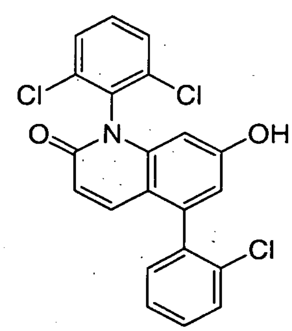
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxy-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxy-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 6**), N-bromosuccinimide, and 2,2'-azobis(2-methylpropionitrile) by a procedure analogous to that described in **INTERMEDIATE 4**. Mass spectrum (ESI) 430.0 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.62 (m, 3H); 7.30-7.49 (m, 5H); 6.77 (d, J=2.0 Hz, 1H); 6.61 (d, J=9.5 Hz, 1H); 6.03 (d, J=2.5 Hz, 1H); 3.74 (s, 3H).

INTERMEDIATE 9

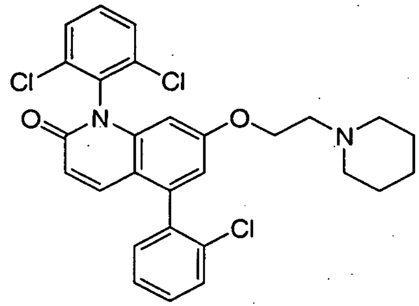
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 8**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 416.05 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.56 (m, 3H); 7.31-7.41 (m, 5H); 6.63 (d, J=2.0 Hz, 1H); 6.46 (d, J=9.5 Hz, 1H); 5.97 (d, J=2.0 Hz, 1H).

EXAMPLE 5

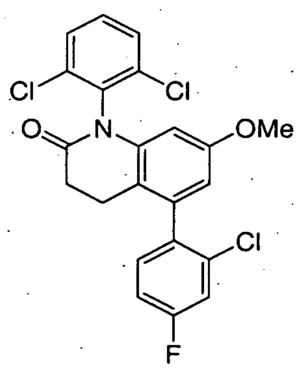
1-(2,6-Dichlorophenyl)-5-(2,5-difluorophenyl)-7-[2-(1-piperidinyl)ethoxy]-2(1*H*)-quinolinone



1-(2,6-Dichlorophenyl)-5-(2,5-difluorophenyl)-7-[2-(1-piperidinyl)ethoxy]-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-2(1H)-quinolinone (**INTERMEDIATE 9**), Ph_3P, 1-piperidine ethanol, and diethyl azodicarboxylate by a procedure analogous to that described in **EXAMPLE 2**. Mass spectrum (ESI) 527.1 (M+1). ^{1}H NMR (500MHz, CDCl3): δ 7.50-7.61 (m, 3H); 7.36-7.47 (m, 5H); 6.75 (d, J=2.5 Hz, 1H); 6.53 (d, J=9.5 Hz, 1H); 6.02 (d, J=2.0 Hz, 1H); 4.00 (t, J= 6.0 Hz 2H); 2.69 (t, J= 6.0 Hz 2H); 2.42 (br s, 4H); 1.45-1.65 (m, 6H).

INTERMEDIATE 10

5-(2-Chloro-5-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone

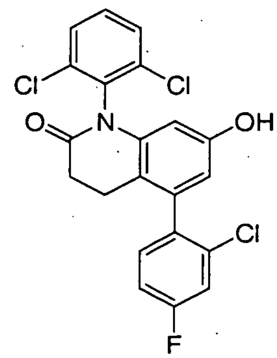


5-(2-Chloro-5-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone was prepared from 5-bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 1**) and 2-chloro-5-

fluorophenylboronic acid by a procedure analogous to that described in **INTERMEDIATE 2**. Mass spectrum (ESI) 450.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.52 (dd, J=3.0 Hz, 8.0 Hz, 2H); 7.25-7.42 (m, 3H); 7.10 (dt, J=2.5 Hz, 1H); 6.47 (d, J=2.0 Hz, 1H); 5.91 (d, J=2.5 Hz, 1H); 3.70 (s, 3H), 2.62-2.89 (m, 4H).

INTERMEDIATE 11

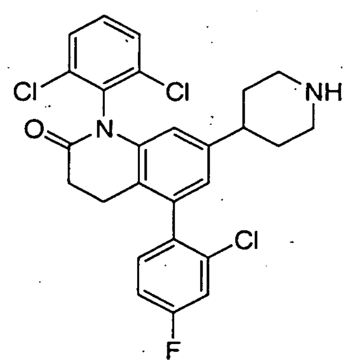
5-(2-Chloro-5-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone



5-(2-Chloro-5-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone was prepared from 5-(2-chloro-5-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 10**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 438.1 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.49 (d, J= 7.5 Hz, 2H); 7.36 (t, J= 8 Hz, 1H); 7.27 (m, 2H); 7.07 (m, 1H); 6.38 (s, 1H); 5.83 (s, 1H); 2.73 (m, 4H).

EXAMPLE 6

1-(2,6-Dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-3,4-dihydro-7-(piperidinyl)-2(1*H*)-quinolinone



Step A: 5-(2-Chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone

5-(2-Chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone was prepared from 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 9**) by a procedure analogous to that described in **EXAMPLE 1**, Step A. Mass spectrum (ESI) 568.0 (M+1).

Step B: 7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone

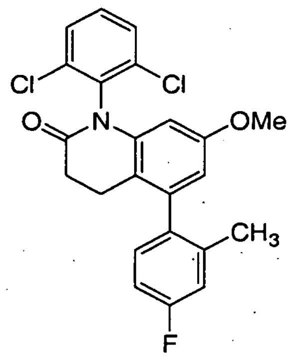
7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone was prepared from 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step B. Mass spectrum (ESI) 603.1 (M+1).

Step C: 5-(2-Chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone

5-(2-Chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-2(1*H*)-quinolinone was prepared from 7-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step C. Mass spectrum (ESI) 505.2 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.52 (d, J= 7.5 Hz, 2H); 7.36 (t, J=8 Hz, 1H); 7.28 (m, 2H); 7.08 (m, 1H); 6.78 (s, 1H); 6.14 (s, 1H); 3.12 (d, J=12 Hz, 2H); 2.71 (m, 6H); 2.49 (m, 2H); 1.74 (d, J=12.5 Hz, 2H); 1.50 (m, 2H).

INTERMEDIATE 12

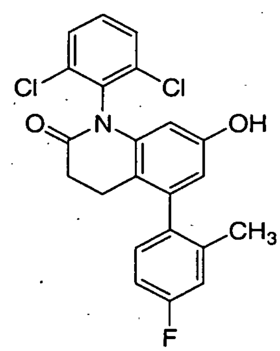
1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-methoxy-2(1*H*)-quinolinone



1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-methoxy-2(1*H*)-quinolinone was prepared from 5-bromo-1-(2,6-dichlorophenyl)-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 1**) and 4-fluoro-2-methylphenylboronic acid by a procedure analogous to that described in **INTERMEDIATE 2**. Mass spectrum (ESI) 430.1 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.50 (m, 2H); 7.36 (m, 1H); 7.17 (m, 1H); 6.98 (m, 2H); 6.45 (s, 1H); 5.89 (s, 1H); 3.69 (s, 3H); 2.72 (m, 4H); 2.15 (s, 3H).

INTERMEDIATE 13

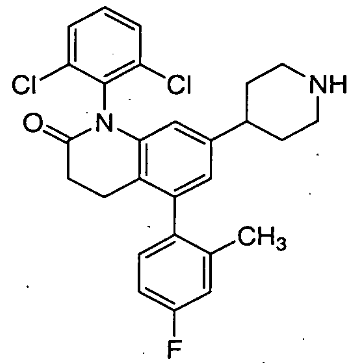
1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-hydroxy-2(1*H*)-quinolinone



1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-hydroxy-2(1*H*)-quinolinone was prepared from 1-(2,6-dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-methoxy-2(1*H*)-quinolinone (**INTERMEDIATE 12**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 416.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.56 (m, 3H); 7.44 (m, 1H); 7.37 (m, 1H); 7.02 (m, 2H); 6.76 (s, 1H); 6.58 (d, J=10 Hz, 1H); 6.01 (s, 1H); 3.73 (s, 3H).

EXAMPLE 7

1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(piperidinyl)-2(1*H*)-quinolinone



Step A: 1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone

1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone was prepared from 1-(2,6-dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 13**) by a procedure analogous to that described in **EXAMPLE 1**, Step A. Mass spectrum (ESI) 548.1 (M+1).

Step B: 7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)- 2(1*H*)-quinolinone

7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)- 2(1*H*)-quinolinone was prepared from 1-(2,6-dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step B. Mass spectrum (ESI) 581.2 (M+1).

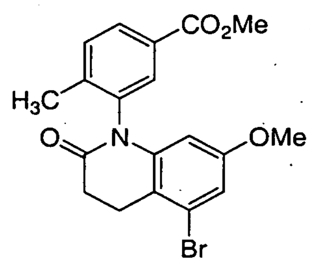
Step C: 1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(4-piperidinyl)-2(1*H*)-quinolinone

1-(2,6-Dichlorophenyl)-3,4-dihydro-5-(4-fluoro-2-methylphenyl)-7-(4-piperidinyl)-2(1*H*)-quinolinone was prepared from 7-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-5-(5-fluoro-2-methylphenyl)- 2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step C. Mass spectrum (ESI) 483.2 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.41 (d, J= 8.5 Hz, 2H); 7.28 (t, J= 8 Hz, 1H); 7.03 (m, 1H); 6.85 (m, 2H);

6.65 (s, 1H); 6.00 (s, 1H); 3.02 (d, J= 12 Hz, 2H); 2.61 (m, 6H); 2.36 (m, 1H); 2.00 (s, 3H); 1.64 (m, 2H); 1.39 (m, 2H).

INTERMEDIATE 14

5-Bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone



Step A: *N*-(3-Methoxycarbonyl-6-methylphenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide

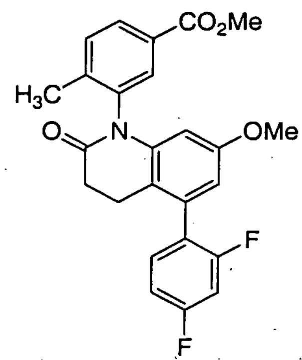
To a solution of 2.00g of 3-(2,6-dibromo-4-methoxyphenyl)-propionic acid (**INTERMEDIATE 1**, Step C), 1.25g of 1(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 361mg of DMAP in 100mL of CH_2Cl_2 was added 1.95g of methyl 3-amino-4-methylbenzoate. The resulting mixture was stirred at room temperature overnight, then concentrated and recrystallized from EtOH to yield 1.85g (64%) of *N*-(3-Methoxycarbonyl-6-methylphenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide as a white solid. Mass spectrum (ESI) 486.0 (M+1). ^{1}H NMR (500MHz, DMSO-d6): δ 9.46 (s, 1H); 8.10 (br s, 1H); 7.65 (br d, J=2.1 Hz, 1H); 7.35 (d, J=3.2 Hz, 1H); 7.27 (s, 2H); 3.83 (s, 3H); 3.77 (s, 3H); 3.17 (m, 2H); 2.76 (m, 2H); 2.63 (s, 3H).

Step B: 5-Bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone

5-Bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from *N*-(3-methoxycarbonyl-6-methylphenyl)-3-(2,6-dibromo-4-methoxyphenyl)-propionamide by a procedure analogous to that described in **INTERMEDIATE 1**, Step E. Mass spectrum (ESI) 374.0 (M-OMe). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.02 (dd, J=2.0, 8.0 Hz, 1H); 7.80 (d, J=8.5 Hz, 1H); 6.80 (d, J=2.5 Hz, 1H); 5.73 (d, J=2.5 Hz, 1H); 3.89 (s, 3H); 3.63 (s, 3H); 3.16 (m, 2H); 2.80 (m, 2H); 2.13 (s, 3H).

INTERMEDIATE 15

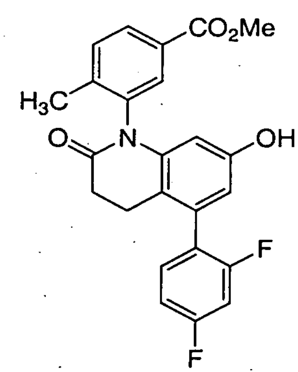
5-(2,4-Difluorophenyl)-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone



5-(2,4-Difluorophenyl)-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from 5-bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone (**INTERMEDIATE 14**) and 2,5-difluorophenylboronic acid by a procedure analogous to that described in **INTERMEDIATE 2**. Mass spectrum (ESI) 438.1 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.06 (d, J=5.0 Hz, 1H); 7.89 (s, 1H); 7.42 (d, J=5.0 Hz, 2H); 7.01 (m, 2H); 6.49 (s, 1H); 5.86 (s, 1H); 3.95 (s, 3H); 3.68 (s, 3H); 2.81 (m, 4H); 2.21 (s, 3H).

INTERMEDIATE 16

5-(2,4-Difluorophenyl)-3,4-dihydro-7-hydroxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone

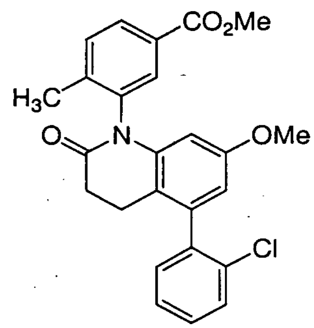


5-(2,4-Difluorophenyl)-3,4-dihydro-7-hydroxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from 5-bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone

(**INTERMEDIATE 15**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 424.1 (M+1). ^{1}H NMR (500MHz, DMSO-d6): δ 9.44 (s, 1H); 7.96 (d, J=8.0 Hz, 1H); 7.75 (s, 1H); 7.59 (d, J=8.0 Hz, 1H); 7.41 (m, 2H); 7.18 (t, J=6.0 Hz, 2H); 6.33 (s, 1H); 5.63 (s, 1H); 3.84 (s, 3H); 2.61 (m, 4H); 2.09 (s, 3H).

INTERMEDIATE 17

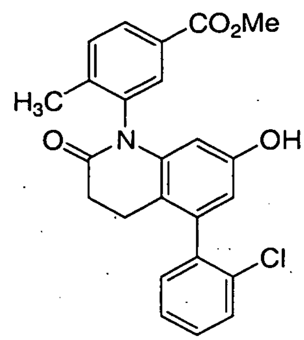
5-(2-Chlorophenyl)-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from 5-bromo-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone (**INTERMEDIATE 16**) and 2-chlorophenylboronic acid by a procedure analogous to that described in **INTERMEDIATE 2**. Mass spectrum (ESI) 436.3 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): 7.95 (m, 1H); 7.81 (d, J=19.0 Hz, 1H); 7.41 (m, 1H); 7.37 (d, J=8.0 Hz, 1H); 7.27 (m, 2H); 7.21 (m, 1H); 6.35 (s, 1H); 5.76 (s, 1H); 3.81 (s, 3H); 3.55 (s, 3H); 2.65 (m, 4H); 2.11 (d, J=11.5 Hz, 3H).

INTERMEDIATE 18

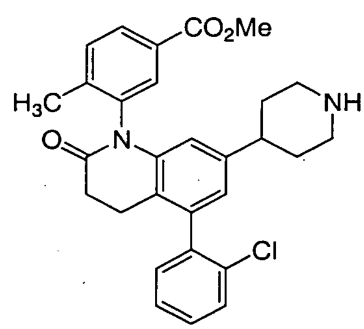
5-(2-Chlorophenyl)-3,4-dihydro-7-hydroxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone



5-(2-Chlorophenyl)-3,4-dihydro-7-hydroxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-3,4-dihydro-7-methoxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone (**INTERMEDIATE 17**) by a procedure analogous to that described in **INTERMEDIATE 3**. Mass spectrum (ESI) 422.2 (M+1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.93 (d, J=7.5 Hz, 1H); 7.85 (d, J=17.5 Hz, 1H); 7.49 (m, 3H); 7.7.26 (m, 1H); 6.34 (s, 1H); 5.78 (s, 1H); 3.85 (s, 3H); 2.62 (m, 4H); 2.14 (d, J=10.5 Hz, 3H).

EXAMPLE 8

5-(2-Chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(4-piperidinyl)-2(1*H*)-quinolinone



Step A: 5-(2-Chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone

5-(2-Chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-3,4-dihydro-7-hydroxy-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone (**INTERMEDIATE 18**) by a procedure analogous to that described in **EXAMPLE 1**, Step A. Mass spectrum (ESI) 554.2 (M+1).

Step B: 7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone

7-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone was prepared from 5-(2-chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(trifluoromethylsulfonato)-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step B. Mass spectrum (ESI) 531.2 (M - tBu).

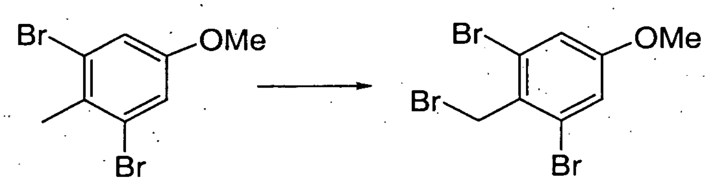
Step C: 5-(2-Chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(4-piperidinyl)-2(1*H*)-quinolinone

5-(2-Chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-7-(4-piperidinyl)-2(1*H*)-quinolinone was prepared from 7-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydro-4-pyridinyl)-5-(2-chlorophenyl)-3,4-dihydro-1-(3-methoxycarbonyl-6-methylphenyl)-2(1*H*)-quinolinone by a procedure analogous to that described in **EXAMPLE 1**, Step C. Mass spectrum (ESI) 489.2 (M+1).

^{1}H NMR (500MHz, $CDCl_3$): δ 7.84 (d, J=23 Hz, 1H); 7.45 (m, 2H); 7.31 (m, 2H); 7.25 (m, 1H); 6.74 (s, 1H); 6.05 (s, 1H); 3.87 (s, 3H); 3.08 (m, 2H); 2.67 (m, 6H); 2.37 (m, 1H); 2.16 (d, J=14 Hz, 3H); 1.67 (m, 2H); 1.44 (m, 2H).

INTERMEDIATE 19

2-bromomethyl-1,3-dibromo-5-methoxy-benzene

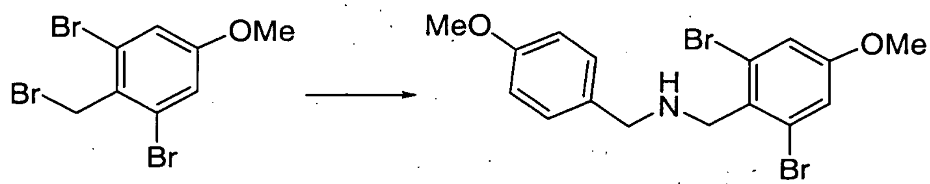


To a solution of 1,3-dibromo-5-methoxy-2-methyl-benzene (16.50g, 58.9mmol) in 300mL of anhydrous CCl_4 under a nitrogen atmosphere was added N-bromosuccinimide (12.59g, 70.7mmol) and benzoyl peroxide (1.57g, 6.5mmol). The solution was then heated to reflux. Once the solution reached reflux it was irradiated with a 250W sun lamp. After 3.5h the solution was cooled to RT and concentrated. To the residue was added ca. 50mL DCM and the resulting suspension filtered. The filtrate was purified by silica gel chromatography (450g SiO_2) using 5% DCM in hexanes as the eluent to give 2-bromomethyl-1,3-dibromo-5-methoxy-benzene. ^{1}H

NMR($CDCl_3$, 500MHz): δ 3.81 (s, 3H), 4.83 (s, 2H), 7.13 (s, 2H). MS(ES) 277 (M-Br); LC 1: 3.93min.

INTERMEDIATE 20

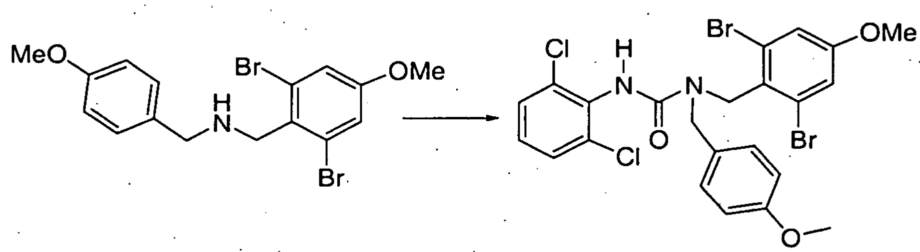
N,N-[(2,6-dibromo-4-methoxyphenyl)methyl]-[(4-methoxyphenyl)methyl]



A solution of 2-bromomethyl-1,3-dibromo-5-methoxy-benzene (20.30g, 56.6mmol) (**INTERMEDIATE 19**) in 100mL of DMF was added to a solution of 4-methoxybenzylamine (19.40g, 141mmol) and potassium carbonate (11.73g, 85.9mmol) in 100mL DMF chilled in an ice bath. The rate of addition was controlled to maintain the internal temperature at 5°C or less. After the completion of the addition the solution was allowed to warm to RT and stirred overnight. The solution was poured into 2L of water and extracted with ethyl ether (3 x 700ml). The combined organics were washed with 1L $NaHCO_3$, 500mL water (3x) and 1L of brine. The solution was dried over Na_2SO_4, filtered and concentrated. The residue (ca. 25g) was purified by silica gel chromatography (550g SiO_2) using 10 to 35% ethyl ether in hexanes as the eluent to give N,N-[(2,6-dibromo-4-methoxyphenyl)methyl]-[(4-methoxyphenyl)methyl]. ^1H NMR($CDCl_3$, 500MHz): δ 3.79 (s, 3H), 3.807 (s, 2H), 3.813 (s, 3H), 4.10 (s, 2H), 6.88 (d, 2H, J=8.5Hz), 7.11 (s, 2H), 7.32 (d, 2H, J=8.5Hz). MS(ES) 414 (M+1); LC 1: 2.32min.

INTERMEDIATE 21

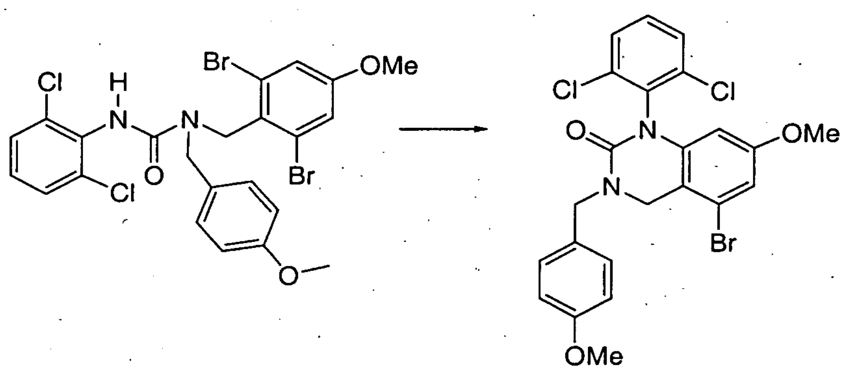
N-[(2,6-dibromo-4-methoxyphenyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea



To a solution of N,N-[(2,6-dibromo-4-methoxyphenyl)methyl]-[(4-methoxyphenyl)methyl] (22.10g, 0.053mol) (**INTERMEDIATE 20**) and N,N-diisopropylethyl amine (12.0ml, 0.064mol) in 200mL of DCM under a nitrogen atmosphere was added solid 2,6-dichlorophenyl isocyanate (10.0g, 0.053mol). An additional 300mL DCM was added to assist in stirring. After ca. 30min. an additional 0.5g of 2,6-dichlorophenyl isocyanate was added and the solution was stirred overnight. The solution was then concentrated to give a white solid which was suspended in 500mL of 1/1 ethyl ether/hexanes. The solution was concentrated again and the resulting solid suspended in 200mL 1/1 ethyl ether/hexanes. The suspension was filtered and the recovered solid washed with ethyl ether/hexanes (1/1) and air dried to give N-[(2,6-dibromo-4-methoxyphenyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.80 (s, 6H), 4.46 (s, 2H), 5.13 (s, 2H), 6.22 (s, 1H), 6.86 (d, 2H, J=8.6Hz), 7.06 (t, 1H, J=8.6Hz), 7.28 (s, 2H), 7.30 (d, 2H, J=8.0Hz). MS(ES) 601 (M+1); LC 1: 3.96min.

INTERMEDIATE 22

1-(2,6-dichlorophenyl)-3-(4-methoxyphenyl)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

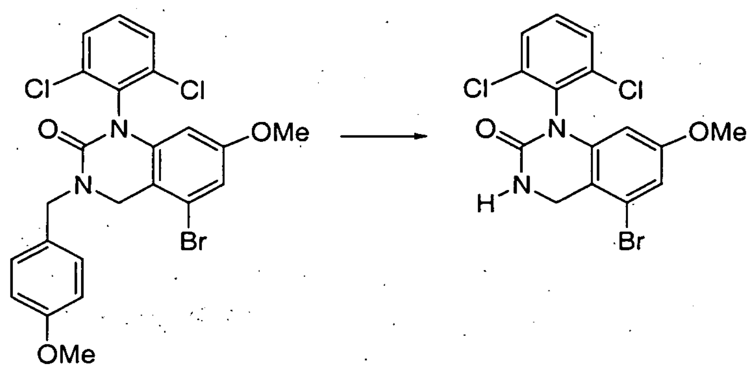


To a flask containing dry, finely ground potassium carbonate (22.17g, 0.160mol) under a nitrogen atmosphere was added anhydrous DMF (800ml), N-[(2,6-dibromo-4-methoxyphenyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea (32.25g, 0.0535mol) (**INTERMEDIATE 21**) and copper iodide (6.80g, 0.0353mol). After refluxing one hour the solution was cooled to RT and poured into a solution containing 700mL NH_4OH (28%) and water (8L). The precipitated product was filtered, washed with water (5 x 500mL), hexanes (4 x 500mL) and air dried to give 1-(2,6-dichlorophenyl)-3-(4-methoxyphenyl)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz):

δ 3.67 (s, 3H), 3.83 (s, 3H), 4.44 (s, 2H), 4.68 (s, 2H), 5.59 (d, 1H, J=2.3Hz), 6.74 (d, 1H, J=2.3Hz), 6.91 (d, 2H, J=8.7Hz), 7.34-7.37 (m, 3H), 7.50 (d, 2H, J=8.0Hz). MS(ES) 521 (M+1); LC 1: 4.15min.

INTERMEDIATE 23

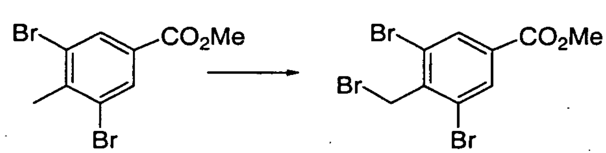
1-(2,6-dichlorophenyl)- 5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone



A solution of 1-(2,6-dichlorophenyl)-3-(4-methoxyphenyl)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (30.91g, 0.0592mol) (**INTERMEDIATE 22**) and anisole (28ml, 0.258mol) in 350mL trifluoroacetic acid under a nitrogen atmosphere was refluxed for 2h. The solution was cooled to RT and concentrated. The residue was partitioned between 500mL $NaHCO_3$ and 500mL EtOAc. The organic phase was washed with water (500mL) and brine (500mL) and concentrated. The $NaHCO_3$ and brine phases contained a suspension of precipitated product. This material was collected by filtration and combined with the crude. The combined crude was suspended in ethyl ether, filtered and washed with ethyl ether and hexanes to give 1-(2,6-dichlorophenyl)- 5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.68 (s, 3H), 4.64 (s, 2H), 5.46 (s, 1H), 5.62 (d, 1H, J=2.3Hz), 6.79 (d, 1H, J=2.5Hz), 7.36 (t, 1H, J=8.1Hz), 7.50 (d, 2H, J=8.2Hz). MS(ES) 401 (M+1); LC 1: 3.18min.

INTERMEDIATE 24

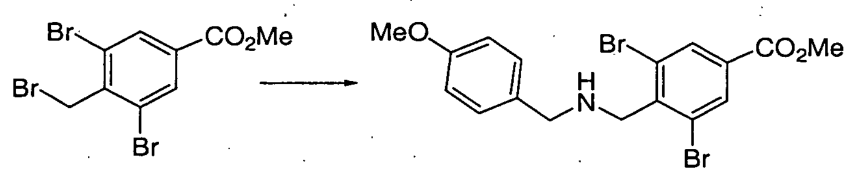
Methyl-4-bromomethyl-3,5-dibromo-benzoate



To a solution of methyl 3,5-dibromo-4-methylbenzoate (150.0g, 0.487mol) in 2L anhydrous CCl_4 under a nitrogen atmosphere was added N-bromosuccinimide (125.7g, 0.706mol) and benzoyl peroxide (12.98g, 0.054mol). The solution was then heated to reflux. Once the solution reached reflux it was irradiated with a 250W sun lamp. After 6h the solution was cooled to RT and filtered. The precipitate (succinimde) was washed with DCM and the filtrate concentrated. The residue (ca. 246g) was purified by silica gel chromatography (3Kg SiO_2) using 5 to 25% DCM/hexanes as the eluent to give methyl-4-bromomethyl-3,5-dibromo-benzoate. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.93 (s, 3H), 4.84 (s, 2H), 8.21 (s, 2H). MS(ES) 385 (M+1); LC 1: 3.93min.

INTERMEDIATE 25

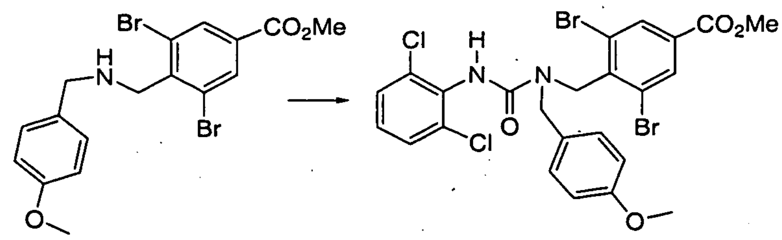
N,N-[(2,6-dibromo-4-methylcarboxylate)methyl]-[(4-methoxyphenyl)methyl]



A solution of methyl 4-bromomethyl-3,5-dibromo-benzoate (188.44g, 0.425mmol) (INTERMEDIATE 24) in 1.6L DMF was added to a solution of 4-methoxybenzylamine (127mL, 0.972mol) and potassium carbonate (67.32g, 0.487mol) in 900mL DMF chilled in an ice bath. The rate of addition was controlled to maintain the internal temperature at 5°C or less. After the addition was complete the solution was warmed to RT and stirred 2 days. The solution was partitioned between 24L water and 6L ethyl ether. Solid sodium chloride was added to assist in the separation of phases. The phases were separated and the aqueous extracted with 4L ethyl ether. The combined organics were washed with 2L $NaHCO_3$, 2L water, 2L brine and dried over Na_2SO_4. The solution was filtered and concentrated to give N,N-[(2,6-dibromo-4-methylcarboxylate)methyl]-[(4-methoxyphenyl)methyl]. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.80 (s, 2H), 3.81 (s, 3H), 3.94 (s, 3H), 4.17 (s, 2H), 6.87 (d, 2H, J=8.7Hz), 7.29 (d, 2H, J=9.0Hz), 8.19 (s, 2H). MS(ES) 442 (M+1); LC 1: 2.22min.

INTERMEDIATE 26

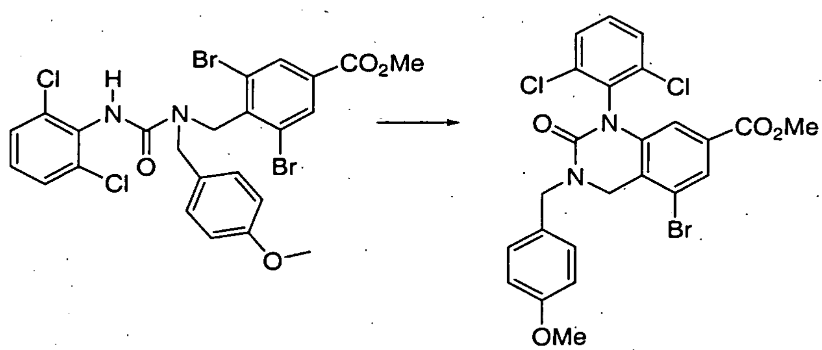
N-[(2,6-dibromo-4-methylcarboxyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea



To a solution of N,N-[(2,6-dibromo-4-m)methyl]-[(4-methoxyphenyl)methyl] (215.86g, 0.487mol) (**INTERMEDIATE 25**) and N,N-diisopropylethyl amine (96.7mL, 0.556mol) in 3L of DCM under a nitrogen atmosphere was added solid 2,6-dichlorophenyl isocyanate (99.8g, 0.531mol). After ca. 2h the solution was concentrated and the residue suspended in 1L 1/1 ethyl ether/hexanes. The solution was filtered and the solid washed with ethyl ether/hexanes (1/1) and air dried to give N-[(2,6-dibromo-4-methylcarboxyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea. The filtrate was concentrated and the residue treated with 500mL ethyl ether/hexanes (1/1). The suspension was filtered and the solid washed with ether/hexanes (1/1) to give additional N-[(2,6-dibromo-4-methylcarboxyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.79 (s, 3H), 3.94 (s, 3H), 4.46 (s, 2H), 5.22 (s, 2H), 6.26 (s, 1H), 6.84 (d, 2H, J=8.6Hz), 7.07 (t, 1H, J=8.1Hz), 7.18 (d, 2H, J=8.6Hz), 7.29 (d, 2H, J=7.2Hz), 8.20 (s, 2H). MS(ES) 629 (M+H); LC 1: 3.94 min.

INTERMEDIATE 27

<u>1-(2,6-dichlorophenyl)-3-(4-methylcarboxylate)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone</u>

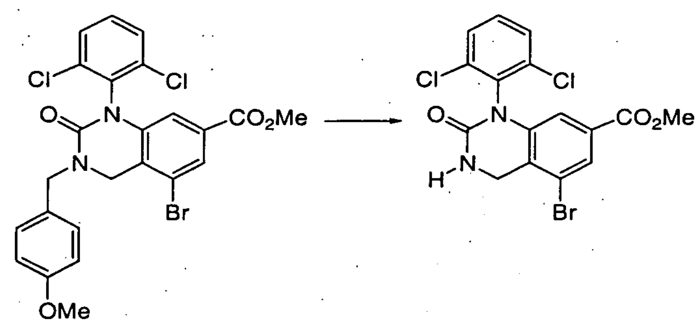


N-[(2,6-dibromo-4-methylcarboxyl)methyl]-N'-(2,6-dichlorophenyl)-N-[(4-methoxyphenyl)methyl]urea (10.0g, 15.8mmol) (**INTERMEDIATE 26**),

copper iodide (3.32g, 17.4mmol) and N,N-diisopropylethyl amine (4.14mL, 23.8mmol) in 150mL anhydrous DMF under a nitrogen atmosphere was heated at 100°C. After 13h the solution was cooled to RT and partitioned between 800mL water and 500mL ether. The mixture was filtered and the residue washed with ethyl ether. The two layers of the filtrate were separated and the organic phase washed with 500mL water (3x), 500mL brine and dried over $MgSO_4$. The solution was treated with charcoal, filtered through solka flock, and concentrated. The residue (white solid) was suspended in hexanes, filtered and air dried to give 1-(2,6-dichlorophenyl)-3-(4-methylcarboxylate)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone. The filtrate was concentrated and the solid residue suspended in hexanes, filtered and air dried to give additional 1-(2,6-dichlorophenyl)-3-(4-methylcarboxylate)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): δ 3.83 (s, 6H), 4.53 (s, 2H), 4.69 (s, 2H), 5.32 (s, 1H), 6.65 (s, 1H), 6.92 (d, 2H, J=8.5Hz), 7.36 (d, 2H, J=8.5Hz), 7.40 (t, 1H,J=8.2Hz), 7.54 (d, 2H, J=8.2Hz), 7.86 (s, 1H). MS(ES) 549 (M+H); LC 1: 4.05min.

INTERMEDIATE 28

1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone



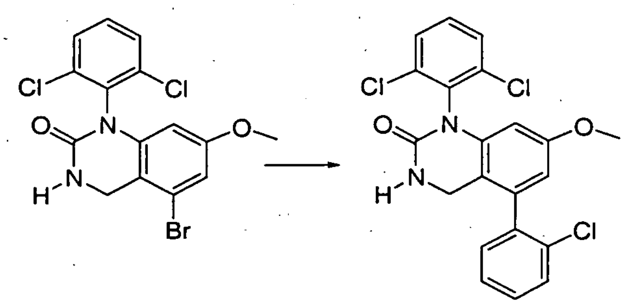
A solution of 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (100g, 0.182mol) (**INTERMEDIATE 27**) and anisole (85.9mL, 0.790mol) in 1132mL trifluoroacetic acid under a nitrogen atmosphere was refluxed for 2h. The solution was cooled to RT and concentrated. The residue was partitioned between 2.5L $NaHCO_3$ and 3L of EtOAc. The phases were separated and the aqueous extracted with 1.5L EtOAc. The combined organics were washed with 1L water, 1L brine, dried over $MgSO_4$, filtered and concentrated. The residue was suspended in hexanes and filtered. The recovered solid was washed with hexanes and

air dried to give 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone.

The aqueous phases, which contained a suspension of the product, were filtered. The recovered solid was washed with water (2x) and hexanes (2x). The recovered solid was then dissolved in a solution of 2L EtOAc and 6L DCM. This solution was then treated with 2L water and enough $NaHCO_3$ to bring the aqueous to ca. pH 8. The layers were separated and the organic phase dried over $MgSO_4$, filtered and concentrated. The solid residue was suspended in hexanes, filtered, washed (hexanes) and air dried to give additional1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): 3.84 (s, 3H), 4.74 (d, 2H, J=1.6Hz), 5.80(s, 1H), 6.68 (d, 1H, J=1.3Hz), 7.41 (t, 1H, J=7.6Hz), 7.53 (d, 2H, J=7.7Hz), 7.91 (d, 1H, J=1.4Hz). MS(ES) 429 (M+H); LC 1: 3.01 min.

INTERMEDIATE 29

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone



Palladium tetrakis triphenylphosine (140mg, 0.12mmol) was added to 1-(2,6-dichlorophenyl)-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (1.02g, 2.54mmol) (**INTERMEDIATE 23**), 2-chlorophenyl boronic acid (642mg, 4.11mmol) and sodium carbonate (436mg, 4.11mmol) in 150mL toluene, 40mL EtOH and 40mL water under an argon atmosphere. After refluxing 3h the solution was cooled to RT and partition between water and EtOAc. The organic phase was washed with water (1x) and brine (1x) and dried over $MgSO_4$. The solution was filtered and concentrated. The residue was absorbed on SiO2 and purified by silica gel chromatography using 3 to 5% acetone in DCM to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone as a white solid. ^1H NMR($CDCl_3$, 500MHz): δ 3.68 (s, 3H), 4.17 (d, 1H, J=14.0Hz), 4.36 (d, 1H,

J=14.0Hz), .5.28 (s, 1H), 5.74 (d, 1H, J=2.3Hz), 6.43 (d, 1H, J=2.5Hz), 7.29-7.37 (m, 4H), 7.47-7.51 (m, 3H). MS(ES) 433 (M+H); LC 1: 3.12min.

INTERMEDIATE 30

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 23**) as described in **INTERMEDIATE 29** (replacing 2-chlorophenyl boronic acid with 2-chloro-4-fluorophenyl boronic). [1]H NMR($CDCl_3$, 500MHz): δ 3.67 (s, 3H), 4.19 (app dd, 1H, J=13.9Hz, 1.6Hz), 4.36 (app dd, 1H, J=13.9, 1.4Hz), 5.08 (s, 1H), 5.76 (d, 1H, J=2.3Hz), 6.42 (d, 1H, J=2.3Hz), 7.09 (dt, 1H, J=8.2, 2.5Hz), 7.25-7.33 (m, 2H), 7.37 (t, 1H, J=8.1Hz), 7.52 (d, 2H, J=7.8Hz). MS(ES) 451 (M+H); LC 1: 3.17 min.

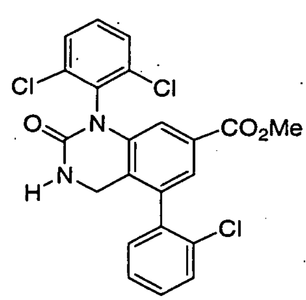
INTERMEDIATE 31

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 23**) as described in **INTERMEDIATE 29** (replacing 2-chlorophenyl boronic acid with 2,4-difluorophenyl boronic). [1]H NMR($CDCl_3$, 500MHz): δ 3.70 (s, 3H), 4.20-4.49 (br m, 2H), 5.23 (s, 1H), 5.76 (d, 1H, J=2.3Hz), 6.48 (d, 1H, J=2.3Hz), 6.92-7.02 (m, 2H), 7.29-32 (m, 1H), 7.37 (t, 1H, J=8.1Hz), 7.52 (d, 2H, J=8.1Hz). MS(ES) 435 (M+H); LC 1: 3.68 min.

INTERMEDIATE 32

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.83 (s, 3H), 4.30 (app dd, 1H, J=15.0, 1.8Hz), 4.49 (app dd, 1H, J=15.3, 1.6Hz), 5.4 (s, 1H), 6.83 (d, 1H, J=1.4Hz), 7.29-7.32 (m, 1H), 7.37-7.43 (m, 3H), 7.51-7.57 (m, 3H), 7.60 (d, 1H, J=1.3Hz). MS(ES) 461 (M+H); LC 1: 3.63min.

INTERMEDIATE 33

1-(2,6-dichlorophenyl)-5-(3-chlorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 3-chlorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.56 (d, 2H, J=1.6Hz), 5.28 (s, 1H), 6.82 (d, 1H, J=1.6Hz), 7.23-7.26 (m, 1H), 7.36-38 (m, 1H), 7.40 (m, 3H), 7.55 (d, 2H, J=8.5Hz), 7.66 (d, 1H, J=1.3Hz). MS(ES) 461 (M+H); LC 1: 3.84min.

INTERMEDIATE 34

1-(2,6-dichlorophenyl)-5-(4-chlorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 4-chlorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.55 (d, 2H, J=1.8Hz), 5.26 (s, 1H), 6.81 (d, 1H, J=1.6Hz), 7.29 (d, 2H, J=8.5Hz), 7.42 (app t, 1H, J=7.7Hz), 7.47 (d, 2H, J=8.3Hz), 7.55(d, 2H, J=8.0Hz), 7.66 (d, 1H, J=1.6Hz). MS(ES) 461 (M+H); LC 1: 3.84min.

INTERMEDIATE 35

1-(2,6-dichlorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) and was isolated as a minor product in the preparation of **INTERMEDIATE 36**. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.73 (s, 2H), 5.34 (s, 1H), 6.77 (d, 1H,

J=1.4Hz), 7.23 (d, 1H, J=7.7Hz), 7.40 (t, 1H, J=7.7Hz) 7.53 (d, 2H, J=8.2Hz), 7.72 (app dd, 1H, J=7.7, 1.4Hz). MS(ES) 351 (M+H); LC 2: 1.99min.

INTERMEDIATE 36

1-(2,6-dichlorophenyl)-5-(2,6-difluorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 2,6-difluorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.46 (d, 2H, J=1.6Hz), 5.21 (s, 1H), 6.86 (d, 1H, J=1.4Hz), 7.04-7.09(m, 2H), 7.38-7.46 (m, 2H), 7.55 (d, 2H, J=8.0Hz), 7.70 (d, 1H, J=0.9Hz). MS(ES) 463 (M+H); LC 1: 3.41min.

INTERMEDIATE 37

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 2,4-difluorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.30-4.61 (br m, 2H), 5.50 (s, 1H), 6.83 (d, 1H, J=1.4Hz), 6.95-7.05 (m, 2H), 7.28-7.43 (m, 1H), 7.42 (app t, 1H, J=7.8Hz), 7.55 (d, 2H, J=8.0Hz), 7.65 (d, 1H, J=1.4Hz). MS(ES) 463 (M+H); LC 1: 3.55 min.

INTERMEDIATE 38

1-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 2-fluorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.83 (s, 3H), 4.30-4.62 (br m, 2H), 5.45 (s, 1H), 6.83 (d, 1H, J=1.6Hz), 7.21 (app t, 1H, J=8.7Hz), 7.26-7.30 (m, 1H), 7.41 (app t, 1H, J=7.8Hz), 7.43-7.47 (m, 1H), 7.55 (d, 2H, J=8.0Hz), 7.68 (d, 1H, J=1.4Hz). MS(ES) 445 (M+H); LC 1: 3.47 min.

INTERMEDIATE 39

1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 4-fluorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.54 (d, 2H, J=1.4Hz), 7.14-7.20 (m, 2H), 7.30-7.34 (m, 2H), 7.41 (app t, 1H, J=7.7Hz), 7.55 (d, 2H, J=8.0Hz), 7.66 (d, 1H, J=1.6Hz). MS(ES) 445 (M+H); LC 1: 3.57 min.

INTERMEDIATE 40

1-(2,6-dichlorophenyl)-5-(2-methylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 2-methylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.83 (s, 3H), 4.21 (app dd, 1H, J=15.3, 1.8Hz), 4.39 (app dd, 1H, J=15.3, 1.6Hz), 5.17 (s, 1H), 6.79 (d, 1H, J=1.4Hz), 7.17 (d, 1H, J=7.3Hz), 7.28-7.37 (m, 3H), 7.42 (app t, 1H, J=7.8Hz), 7.56 (d, 2H, J=8.3Hz), 7.58 (d, 1H, J=1.4Hz). MS(ES) 441 (M+H); LC 1: 3.65 min.

INTERMEDIATE 41

1-(2,6-dichlorophenyl)-5-phenyl-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with phenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.83 (s, 3H), 4.56 (s, 2H), 5.41 (s, 1H), 6.80 (d, 1H, J=1.6Hz), 7.34-7.37 (m, 2H), 7.39-7.50 (m, 4H), 7.55 (d, 2H, J=8.0Hz), 7.69 (d, 1H, J=1.6Hz). MS(ES) 427 (M+H); LC 1: 3.52 min.

INTERMEDIATE 42

1-(2,6-dichlorophenyl)-5-(3-fluorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 3-fluorophenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.84 (s, 3H), 4.56 (d, 2H, J=1.2Hz), 5.55 (s, 1H), 6.81 (d, 1H, J=1.4Hz), 7.04-7.09 (m, 1H), 7.11-7.17 (m, 2H), 7.41 (app t, 1H, J=7.5Hz), 7.44-7.48 (m, 1H), 7.56 (d, 2H, J=8.0Hz), 7.67 (d, 1H, J=1.6Hz). MS(ES) 459 (M+H); LC 1: 3.57min.

INTERMEDIATE 43

1-(2,6-dichlorophenyl)-5-(2-trifluoromethylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 2-trifluoromethylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.83 (s ,3H), 4.20-4.27 (m, 2H), 5.14 (s, 1H), 6.83 (d, 1H, J=1.6Hz), 7.35 (d, 1H, J=7.3Hz), 7.41 (app t, 1H, J=7.8Hz), 7.55 (m, 1H), 7.56 (m, 1H), 7.58-7.62 (m, 2H), 7.65 (app t, 1H, J=7.6Hz), 7.83 (d, 1H, J=7.8Hz). MS(ES) 495 (M+H); LC 1: 3.76min.

INTERMEDIATE 44

1-(2,6-dichlorophenyl)-5-(3-methylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 3-methylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 2.44 (s, 3H), 3.84 (s, 3H), 4.57 (d, 2H, J=1.6Hz), 5.21 (s, 1H), 6.79 (d, 1H, J=1.6Hz), 7.12-7.18 (m, 2H), 7.24-7.27 (m, 1H), 7.36 (t, 1H, J=7.5Hz), 7.41 (app t, 1H, J=7.8Hz), 7.56 (d, 2H, J=8.0Hz), 7.68 (d, 1H, J=1.6Hz). MS(ES) 441 (M+H); LC 1: 3.76min.

INTERMEDIATE 45

<u>1-(2,6-dichlorophenyl)-5-(4-methylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone</u>

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 4-methylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 2.44 (s, 3H), 3.83 (s, 3H), 4.57 (d, 2H, J=1.6Hz), 5.24 (s, 1H), 6.78 (d, 1H, J=1.6Hz), 7.24 (d, 2H, J=8.0Hz), 7.29 (d, 2H, J=7.8Hz), 7.41 (app t1, 1H, J=7.8Hz), 7.55 (d, 2H, J=8.2Hz), 7.68 (d, 1H, J=1.4Hz). MS(ES) 441 (M+H); LC 1: 3.71min.

INTERMEDIATE 46

<u>1-(2,6-dichlorophenyl)-5-(4-trifluoromethylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone</u>

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 4-trifluoromethylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.85 (s, 3H), 4.55 (d, 2H, J=1.9Hz), 5.26 (s, 1H), 6.84 (d, 1H, J=1.6Hz), 7.43 (app 1, 1H, J=7.6Hz), 7.50 (d, 2H, J=8.1Hz), 7.68 (d, 2H, J=8.0Hz), 7.68 (d, 1H, J=1.4Hz), 7.76 (d, 2H, J=8.3Hz). MS(ES) 495 (M+H); LC 1: 3.89min.

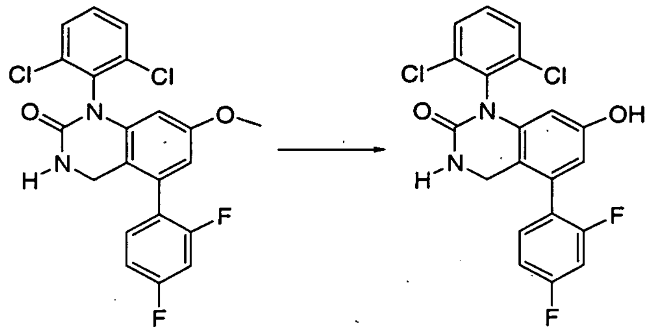
INTERMEDIATE 47

<u>1-(2,6-dichlorophenyl)-5-(3-trifluoromethylphenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone</u>

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-bromo-7-methylcarboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29** (replacing ethanol with methanol and 2-chlorophenyl boronic acid with 3-trifluoromethylphenyl boronic acid). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.85 (s, 3H), 4.55 (d, 2H, J=1.8Hz), 5.17 (s, 1H), 6.84 (d, 1H, J=1.4Hz), 7.43 (app t, 1H, J=7.6Hz), 7.54-7.58 (m, 3H), 7.61-7.65 (m, 2H), 7.68 (d, 1H, J=1.6Hz), 7.71-7.74 (m, 1H). MS(ES) 495 (M+H); LC 1: 3.87min.

INTERMEDIATE 48

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone



Boron tribromide (1.0M DCM, 0.15mL) was added to 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (18mg, 0.041mmol) (**INTERMEDIATE 31**) in 1mL DCM. After 1.2h the solution was partitioned between EtOAc (15ml) and pH 4 buffer (5mL). The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography using EtOAc/Hexanes as the eluent to give 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR(CD_3OD, 500MHz): δ 4.23 (brm, 2H), 5.62 (d, 1H, J=2.1Hz), 6.38 (d, 1H, 2.3Hz), 7.04-7.10 (m, 2H), 7.31-7.38 (m, 1H), 7.48 (t, 1H, J=8.5Hz), 7.61 (d, 2H, J=8.0Hz). MS(ES) 421 (M+H); LC 1: 2.88min.

INTERMEDIATE 49

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 29**) as described in **INTERMEDIATE 48**. ^{1}H NMR(CD_3OD, 500MHz): δ 4.11 (d, 1H, J=14.5Hz), 4.21 (d, 1H, J=14.5Hz), 5.59 (d, 1H, J=2.1Hz), 6.31 (d, 1H, J=2.3Hz), 7.29-7.32 (m, 1H), 7.37-7.42 (m, 2H), 7.46-7.52 (m, 2H), 7.60-7.63 (m, 2H). MS(ES) 419 (M+H); LC 1: 2.96min.

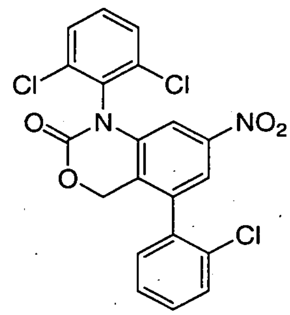
INTERMEDIATE 50

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 30**) as described in **INTERMEDIATE 48**. ^{1}H NMR(DMSO, 500MHz): δ 5.50 (s, 1H); 6.21 (s, 1H); 7.23-7.34 (m, 2H); 7.42 (t, 1H, J=6.5 Hz); 7.51-7.60 (m, 2H); 7.69 (d, 2H, J=8.0 Hz). MS(ES) 437 (M+H); LC 1: 2.73min.

INTERMEDIATE 51

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-nitro-benzoxazin-2-one



Step A: 1-Bromomethyl-2,6-dibromo-4-nitrobenzene .

A mixture of 2,6-dibromo-4-nitrotoluene (3.83g, 1eq.), N-bromosuccinimide (3.23g, 1.4eq.) and dibenzoylperoxide (315mg, 0.1eq.) in CCl_4 was degassed with argon. The mixture was brought to reflux and azobisisobutyronitrile (213mg, 0.1eq.) was added. The mixture was maintained at reflux for 6 hours. The reaction was cooled to room temperature, concentrated and purified to give 1-Bromomethyl-2,6-dibromo-4-nitrobenzene. ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 4.81 (2H, s), 8.41(2H, s).

Step B: 1-Hydroxymethyl-2,6-dibromo-4-nitrobenzene

A mixture of 1-bromomethyl-2,6-dibromo-4-nitrobenzene (4.45g, 1eq.) and $CaCO_3$ (5.7g, 5eq.) in 1,4-dioxane (20mL) and water (20mL) was heated to and maintained at reflux overnight. The mixture was cooled, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrousmgSO_4, filtered and concentrated. The product was purified by silica gel chromatography (eluted with 4:1 hexanes:ethyl acetate) to give 1-Hydroxymethyl-2,6-dibromo-4-nitrobenzene. ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 2.28 (1H, broad t), 5.05(2H, m), 8.397(2H, s).

Step C: 1-(N-(2,6-dichlorophenyl)carbamoyloxymethyl-2,6-dibromo-4-nitrobenzene.

To a solution of 1-hydroxymethyl-2,6-dibromo-4-nitrobenzene (1.73g) in CH_2Cl_2 (30mL) was added 2,6-dichlorophenylisocyanate (1.15g, 1.1eq.). A few crystals of N,N-dimethylaminopyridine were added and the mixture was allowed to stir overnight. The CH_2Cl_2 was removed and the residue dissolved in hot ethyl acetate. The solution was filtered, diluted with hexanes and allowed to crystallize. The crystals were collected and washed with cold 1:1 hexanes:ethyl acetate to yield 1-(N-(2,6-dichlorophenyl)carbamoyloxymethyl-2,6-dibromo-4-nitrobenzene. Mass spectrum (ESI) 496.9 (M+1). ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 5.569 (2H, s), 6.342 (1H boad s), 7.162(1H, t, J=8 Hz), 7.350 (2H, d, J=8 Hz), 8.411 (2H, s).

Step D: <u>1-(2,6-dichlorophenyl)-5-bromo-7-nitro-benzoxazin-2-one</u>

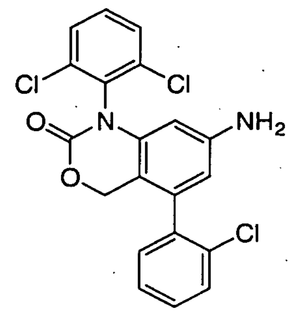
A mixture of 1-(N-(2,6-dichlorophenyl)carbamoyloxymethyl-2,6-dibromo-4-nitrobenzene (25mg, 1eq.) and CuI (20mg, 2eq.) in N,N-dimethylformamide (1mL) was degassed with argon. To the mixture was added N,N-diisopropylethylamine (0.02mL) and the mixture was lowered into a 130°C heating bath. The mixture was heated for 1 hour under argon. The mixture was cooled, filtered and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered, concentrated and purified by preparative thin layer chromatography (eluted with 4:1 hexanes: ethyl acetate) to yield 1-(2,6-dichlorophenyl)-5-bromo-7-nitro-benzoxazin-2-one. Mass spectrum (ESI) 417.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 5.569 (2H, s), 6.964 (1H, d, J=2 Hz), 7.44-7.48 (1H, m), 7.558 (2H, d, J=8 Hz), 8.169 (1H, d, J=2 Hz).

Step E: <u>1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-nitro-benzoxazin-2-one</u>

A mixture of 1-(2,6-dichlorophenyl)-5-bromo-7-nitro-benzoxazin-2-one (96mg, 1 eq.) and 2-chlorophenylboronic acid (44mg, 1.2eq.) in n-butanol (2mL) was degassed with argon. To the mixture was added 1M Na_2CO_3 (1mL) and Pd(dppf)Cl_2•CH_2Cl_2 (10mg, 0.05eq.) and the mixture was lowered into a 90°C heating bath. After 75 minutes the mixture was cooled to room temperature. The mixture was diluted with water and brine and extracted 3x with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by silica gel chromatography (eluted with 8:1 hexanes: ethyl acetate) to yield 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-nitro-benzoxazin-2-one. Mass spectrum (ESI) 449.1 (M+1). ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 5.130 (1H, ½ ABq, J=14.5 Hz), 5.367 (1H, ½ ABq, J=14.5 Hz), 7.100 (1H, d, J=2 Hz), 7.322 (1H, m), 7.40-7.48 (3H, m), 7.54-7.59 (3H, m), 7.905 (1H, d, J=2 Hz).

INTERMEDIATE 52

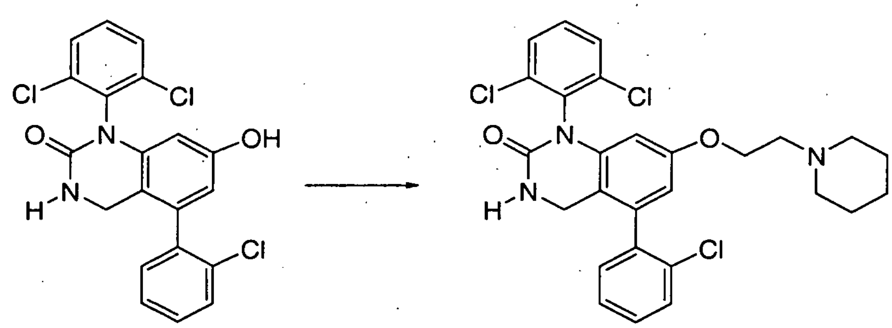
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-amino-benzoxazin-2-one



To a stirred solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-nitro-benzoxazin-2-one (55mg) in ethyl acetate (5mL) was added 10% palladium on carbon (dry weight, approx 50% water) (40mg). Hydrogen gas was bubbled through the mixture for 5 minutes and the mixture was then allowed to stir under a balloon of hydrogen. After 50 minutes the reaction flask was purged with argon. The catalyst was filtered off and washed with methanol. The filtrate was concentrated and purified by preparative thin layer chromatography (eluted 2x with 2:1 hexanes:acetone) to yield 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-amino-benzoxazin-2-one. Mass spectrum (ESI) 419.0 (M+1). ^{1}H NMR (500MHz, $CDCl_3$) δ $CHCl_3$: 4.941 (1H, ½ ABq, J=13 Hz), 5.195 (1H, ½ ABq, J=13 Hz), 5.561 (1H, d, J=2 Hz), 6.288 (1H, d, J=2 Hz), 7.26-7.39 (4H, m), 7.45-7.51 (3H, m).

EXAMPLE 9

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[2-(1-piperidinyl)ethoxy]-3,4-dihydro-2(1H)-quinazolinone

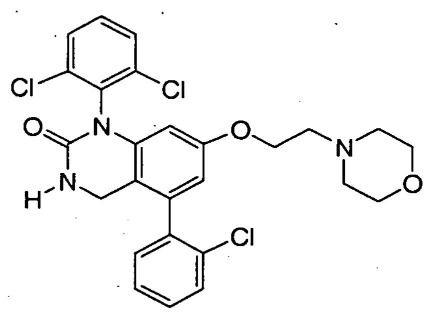


Diethyl azodicarboxylate (50μL, 0.32mmol) was added dropwise to a solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (30mg, 0.07mmol) (**INTERMEDIATE 49**), triphenylphosphine

(95mg, 0.36mmol) and 1-(2-hydroxyethyl)piperidine (55mg, 0.43mmol) in 1mL tetrahydrofuran at 65°C under an argon atmosphere. After 1h the solution was cooled to RT and partitioned between saturated $NaHCO_3$ (5mL) and EtOAc (15mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by thin layer chromatography using EtOAc followed by $CHCl_3/MeOH/NH_4OH$ (87/12/1) as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[2-(1-piperidinyl)ethoxy]-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): δ 1.44 (m, 2H), 1.62 (m, 4H), 2.48 (m, 4H), 2.72 (m, 2H), 4.00 (t, 2H, J=6.0Hz), 4.18 (d, 1H, J=14.0Hz), 4.36 (d, 1H, J=14.0Hz), 5.22 (s, 1H), 5.76 (d, 1H, J=1.8Hz), 6.45 (d, 1H, J=2.0Hz), 7.28-7.39 (m, 4H), 7.45-7.53 (m, 3H). MS(ES) 530 (M+H); LC 1: 2.28 min.

EXAMPLE 10

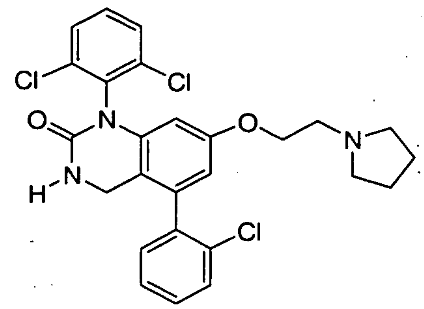
<u>1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[2-(1-morpholinyl)ethoxy]-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared similarly to **EXAMPLE 9** (replacing 1-(2-hydroxyethyl)piperidine with 1-(2-hydroxyethyl)morpholine. ^1H NMR($CDCl_3$, 500MHz): 2.52 (m, 4H), 2.73 (m, 2H), 3.72 (m, 4H), 3.99 (m, 2H), 4.19 (d, 1H, J=14.2Hz), 4.36 (d, 1H, J=14.0Hz), 5.15 (s, 1H), 5.78 (d, 1H, J=2.3Hz), 6.45 (d, 1H, J=2.2Hz), 7.29-7.40(m, 4H), 7.48-7.54 (m, 3H). MS(ES) 532 (M+H); LC 1: 2.07min.

EXAMPLE 11

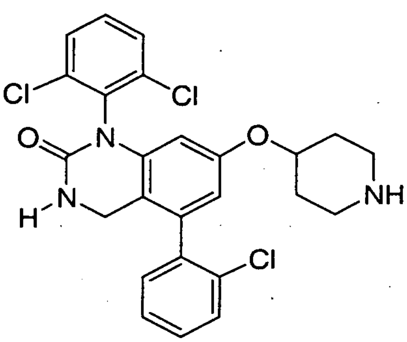
<u>1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[2-(1-pyrrolidinyl)ethoxy]-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared as described in **EXAMPLE 9** (replacing 1-(2-hydroxyethyl)piperidine with 1-(2-hydroxyethyl)pyrrolidine). ^{1}H NMR($CDCl_3$, 500MHz): δ 1.85 (brm, 4H), 2.72 (brm, 4H), 2.93 (t, 2H, J=5.4Hz), 4.05 (t, 2H, J=5.2Hz), 4.19 (d, 1H, 14.2Hz), 4.36 (d, 1H, J=13.9Hz), 5.26 (s, 1H), 5.78 (d, 1H, J=2.3Hz), 6.45 (d, 1H, J=2.3Hz), 7.29-7.38 (m, 4H), 7.48-7.52 (m, 3H). MS(ES) 516.1 (M+H); LC 1: 2.19min.

EXAMPLE 12

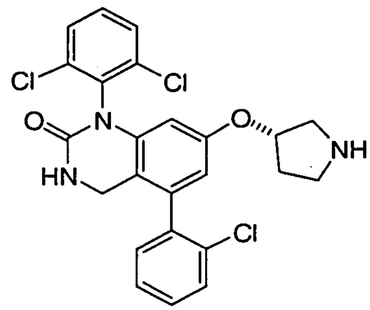
<u>1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(4-piperidinyl)]-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared as described in **EXAMPLE 9** (replacing 1-(2-hydroxyethyl)piperidine with 4-hydoxy-1-Boc-piperidine). The *tert*-butoxycarbonyl carbonyl group was subsequently removed by treatment with 1/1 TFA/DCM as described in **EXAMPLE 34** Step B. ^{1}H NMR(CD_3OD, 500MHz): δ 1.55-1.65 (m, 2H), 1.88-1.96 (m, 2H), 2.64-2.70 (m, 2H), 2.97-3.06 (m, 2H), 4.19 (ABq, 2H, 14.7Hz), 4.25-4.31 (m, 1H), 5.61 (d, 1H, J=2.0Hz), 6.49 (d, 1H, J=2.3Hz), 7.30-7.35 (m, 1H), 7.36-7.43 (m, 2H), 7.46-7.56 (m, 2H), 7.60-7.63 (m, 2H). MS(ES) 543 (M+CH3CN+H), 502 (M+H); LC 1: 2.21min.

EXAMPLE 13

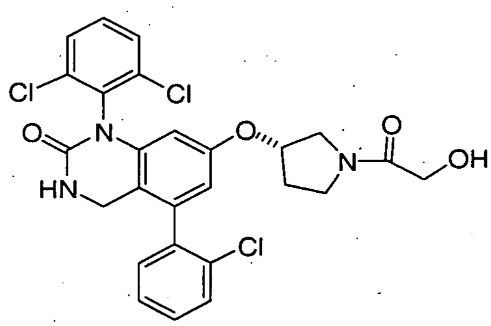
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 9** (replacing 1-(2-hydroxyethyl)piperidine with (R)-3-hydroxy-N-Boc-pyrrolidine). The *tert*-butoxycarbonyl carbonyl group was subsequently removed by treatment with 1/1 TFA/DCM as described in **EXAMPLE 34** Step B. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.86-2.00 (m, 2H), 2.84-2.98 (m, 2H), 3.08-3.18 (m, 2H), 4.19 (d, 1H J=14.2Hz), 4.34 (d, 1H, J=14.0Hz), 4.65 (m, 1H), 5.51 (s, 1H), 5.67 (d, 1H, J=2.1Hz), 6.38 (d, 1H, J=2.0Hz), 7.26-7.31 (m, 1H), 7.32-7.39 (m, 3H), 7.48-7.53 (m, 3H). MS(ES) 488 (M+H); LC 1: 2.01min.

EXAMPLE 14

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(1-hydoxyacetyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone

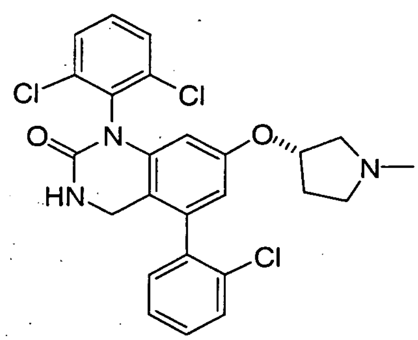


1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (50mg, 0.26mmol) was added to a solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone (40mg, 0.08mmol) (EXAMPLE 13), 1-hydroxybenzotriazole hydrate (35mg, 0.26mmol),

N,N-diisopropylethylamine (0.1ml, 0.57mmol) and glycolic acid (20mg, 0.26mmol) in DCM (1.5ml). After stirring overnight the solution was partitioned between EtOAc and water. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative thin layer chromatography using EtOAc as the eluent to give 15mg of the title compound. ^{1}H NMR($CDCl_3$, 500MHz): selected data, rotamers δ 1.94-2.15 (m, 1H), 2.19-2.35 (m, 2H), 3.39-3.50 (m, 2H), 3.57-3.65 (m, 1H), 3.72-3.89 (m, 1H), 4.00-4.25 (m, 2H), 4.30-4.38 (m, 1H), 4.78-4.88 (m, 1H). MS(ES) 516 (M+H); LC 1: 2.47 min.

EXAMPLE 15

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(1-methyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone

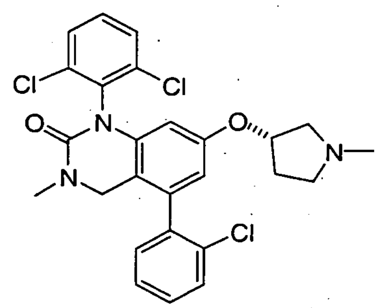


To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone (40mg, 0.082mmol) (**EXAMPLE 13**) in 1.5mL MeOH was added formaldehyde (37%, 100mg, 1.2mmol) followed by sodium cyanoborohydride (80mg, 1.27mmol). After stirring overnight the solution was concentrated and the residue partitioned between EtOAc and 1N NaOH. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (87/12/1). The isolated material contained the title compound along with the corresponding 3-hydroxymethyl product. This material was treated with MeOH and K_2CO_3 (spatula tip) and stirred overnight. The solution was concentrated and the residue partitioned between EtOAc and water. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (91/9/1) to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(1-methyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-

quinazolinone. [1]H NMR($CDCl_3$, 500MHz): δ 1.90-1.98 (m, 1H), 2.13-2.22 (m, 1H), 2.38-2.46 (m, 1H), 2.39 (s, 3H), 2.64-2.74 (m 1H), 2.78-2.88 (m, 2H), 4.18 (d, 1H, J=13.9Hz), 4.34 (d, 1H, J=14.2Hz), 4.67 (brm, 1H), 5.40 (s, 1H), 5.71 (s, 1H), 6.35 (m, 1H), 7.26-7.31 (m, 1H), 7.32-7.39 (m, 3H), 7.48-7.53 (m, 3H). MS(ES) 502 (M+H); LC 1: 2.13 min.

EXAMPLE 16

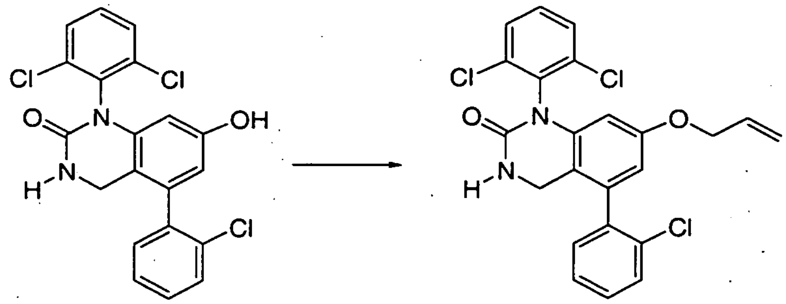
1-(2,6-dichlorophenyl)-3-methyl-5-(2-chlorophenyl)-7-[oxy-(1-methyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone



Sodium hydride (60%, spatula tip, excess) was added to 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[oxy-(1-methyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone (11.9mg, 0.0237mmol) (**EXAMPLE 15**) in 1mL DMF at 0°C. After stirring 10min methyl iodide (0.67M in DMF, 40μL, 0.027mmol) was added. The solution was then stirred at RT for 1.5h. The solution was partitioned between EtOAc and 1N NaOH. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative thin layer chromatography using $CHCl_3$/MeOH/NH_4OH (94/6/1) as the eluent to give 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chlorophenyl)-7-[oxy-(1-methyl-3-(S)-pyrrolidinyl)]-3,4-dihydro-2(1H)-quinazolinone. [1]H NMR($CDCl_3$, 500MHz): δ 1.90-1.98 (m, 1H), 2.12-2.21 (m, 1H), 2.35-2.41 (m, 1H), 2.38 (s, 3H), 2.61-2.70 (m, 1H), 2.78-2.86 (m, 2H), 2.99 (s, 3H), 4.11 (dd, 1H, J=14.4, 2.0Hz), 4.26 (d, 1H, J=14.4Hz), 4.67 (brm, 1H), 5.67 (d, 1H, J=1.9Hz), 6.33 (m, 1H), 7.30-7.40 (m, 4H), 7.49-7.57 (m, 3H). MS(ES) 516 (M+H); LC 1: 2.44min.

INTERMEDIATE 53

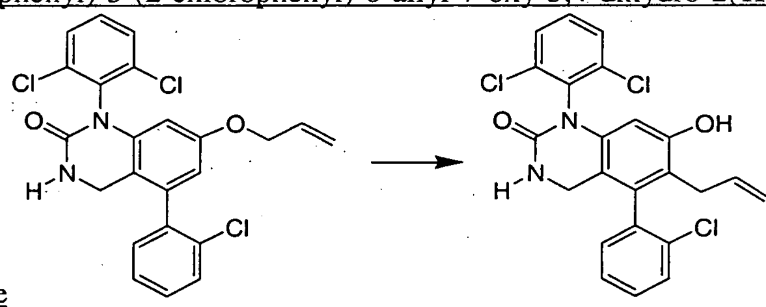
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-allyloxy-3,4-dihydro-2(1H)-quinazolinone



A solution containing 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (259mg, 0.617mmol) (**INTERMEDIATE 49**), potassium carbonate (300mg, 2.2mmol), allyl chloride (0.45mL, 5.53mmol) and sodium iodide (87mg, 0.58mmol) in 15mL acetone was refluxed for seven hours. The solution was concentrated and the residue partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography using 2% acetone in DCM to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-allyloxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 4.18 (d, 1H, 14.2Hz), 4.34 (d, 1H, J=14.2Hz), 4.40 (app d, 2H, J=5.5Hz), 5.20-5.32(m, 2H), 5.77 (d, 1H, J=2.3Hz), 5.82 (s, 1H), 5.90-6.00 (m, 1H), 6.44 (d, 1H, J=2.3Hz), 7.27-7.31 (m, 1H), 7.32-7.38 (m, 3H), 7.48-7.52 (m, 3H). MS(ES) 459 (M+H); LC 1: 3.30 min.

INTERMEDIATE 54

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-allyl-7-oxy-3,4-dihydro-2(1H)-quinazolinone

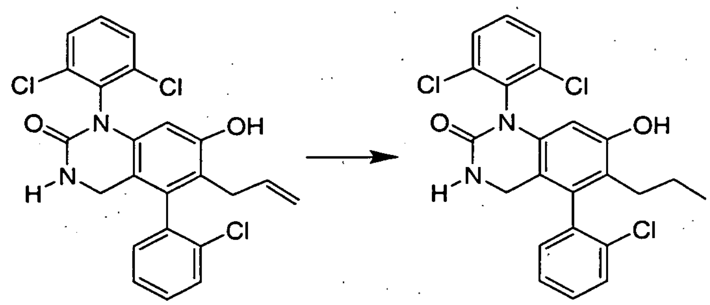


A solution containing 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-allyloxy-3,4-dihydro-2(1H)-quinazolinone (200mg, 0.435mmol) (**INTERMEDIATE 53**) and 2,6-di-*tert*-butyl-4-methylphenol (20mg) in 200mL 1,2,4-trichlorobenzene under an argon atmosphere was refluxed for 10hrs. The solution was cooled to RT and partitioned between acetonitrile and hexanes. The phases were separated and the lower phase (CH_3CN) washed with hexanes (2x). The solution was concentrated and

the residue purified by silica gel chromatography using 70% ethyl ether in hexanes as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-allyl-7-oxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.95 (dd, 1H, J=16.2, 6.4Hz), 3.13 (dd, 1H, J=16.3, 5.9Hz), 4.08 (dd, 1H, J=14.0,1.5Hz), 4.18 (dd, 1H, J=13.9, 1.0Hz), 5.00-5.09 (m, 2H), 5.74 (s, 1H), 5.80-5.87 (m, 1H), 7.21-7.25 (m, 1H), 7.35-7.40 (m, 3H), 7.51-7.55 (m, 3H). MS(ES) 459 (M+H); LC 1: 3.03 min.

INTERMEDIATE 55

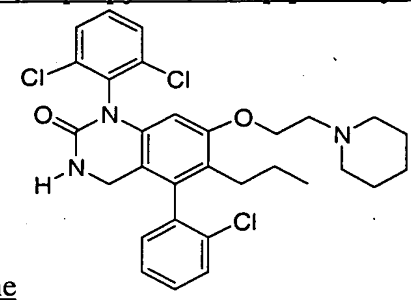
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-propyl-7-oxy-3,4-dihydro-2(1H)-quinazolinone



Platinum(IV) oxide (4mg) was added to a solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-allyl-7-oxy-3,4-dihydro-2(1H)-quinazolinone (20mg, 0.044mmol) (**INTERMEDIATE 54**) in 4mL EtOAc. The solution was stirred under a hydrogen atmosphere (ballon) for 2h. The solution was filtered through Celite and concentrated. The residue was purified by preparative thin layer chromatography using 8% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-propyl-7-oxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR(CD_3OD, 500MHz): δ 0.70 (t, 3H, J=7.3Hz), 1.28-1.44 (m, 2H), 2.01-2.09 (m, 1H), 2.26-2.32 (m, 1H), 4.01 (app d, 2H, J=4.3Hz), 5.67 (s, 1H), 7.24-7.28 (m, 1H), 7.39-7.43 (m, 3H), 7.47 (t, 1H, J=8.0Hz), 7.52-7.56 (m, 1H), 7.59 (d, 2H, J=8.7Hz). MS(ES) 461 (M+H); LC 1: 3.37 min.

EXAMPLE 17

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-propyl-7-[2-(1-piperidinyl)ethoxy]-3,4-

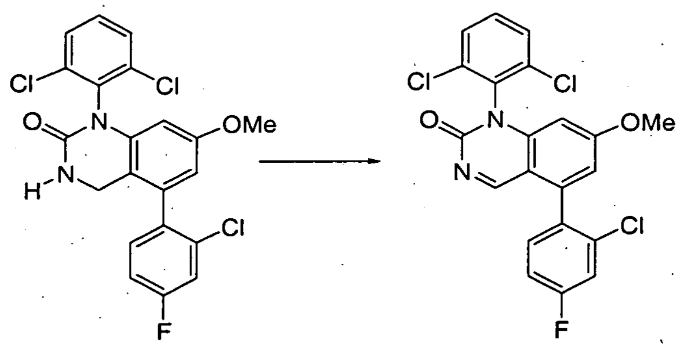


dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-6-propyl-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 55**) as described in **EXAMPLE 9**. ^{1}H NMR($CDCl_3$, 500MHz): 0.74 (t, 3H, J=7.4Hz), 1.25-1.32 (m, 2H), 1.44 (brm, 2H), 1.59(brm, 4H), 2.02-2.11 (m, 1H), 2.88-2.35 (m, 1H), 2.48 (brm, 4H), 2.70 (t, 2H, 5.6Hz), 3.83 (t, 2H, J=5.7Hz), 4.03 (d, 1H, 14.2Hz), 4.16 (d, 1H, J=14.0Hz), 5.16 (s, 1H), 5.66 (s, 1H), 7.21-7.25 (m, 1H), 7.33-7.39 (m, 3H), 7.49-7.53 (m, 3H). MS(ES) 572.2 (M+H); LC 1: 2.64min.

INTERMEDIATE 56

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(methoxy)-2(1H)-quinazolinone



To a solution of 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (112mg, 0.248mmol) (**INTERMEDIATE 30**) in 1,4-dioxane (5mL) at 65°C under an argon atmosphere was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (115mg, 0.51mmol) in 1,4-dioxane (2.5mL). After 2h the solution was cooled to RT and partitioned between $NaHCO_3$ and EtOAc. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel

chromatography using 3 to 5% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(methoxy)-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.70 (s, 3H), 5.94 (d, 1H, J=2.1Hz), 6.74 (d, 1H, J=2.1Hz), 7.18 (app dt, 1H, J=8.1, 2.5Hz), 7.35 (m, 1H), 7.42 (m, 1H), 7.47 (t, 1H, J=8.2Hz), 7.56-7.60 (m, 2H). MS(ES) 449 (M+H); LC 1: 3.40min.

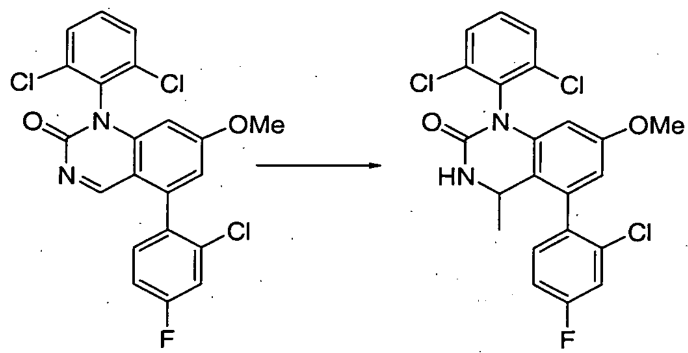
INTERMEDIATE 57

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(methoxy)-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 29**) as described in **INTERMEDIATE 56**. ^{1}H NMR($CDCl_3$, 500MHz): δ 3.81 (s, 3H), 5.95 (d, 1H, J=2.3Hz0), 6.79 (d, 1H, J=2.1Hz), 7.40-7.51 (m, 4H), 7.55-7.63 (m, 3H), 8.78 (s, 1H). MS(ES) 431 (M+H); LC 1: 3.47 min.

INTERMEDIATE 58

1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

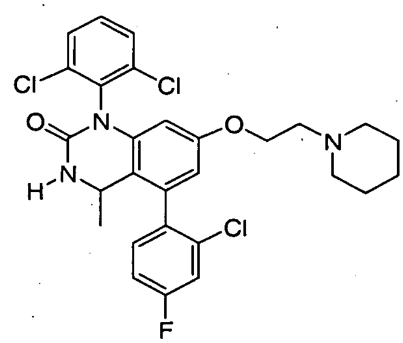


A solution of methylmagnesium bromide (3.0M ethyl ether, 0.5mL) was added dropwise to 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(methoxy)-2(1H)-quinazolinone (230mg, 0.511mmol) (**INTERMEDIATE 56**) in THF (10mL) at –78C. After 20min the solution was warmed to 0°C. After 40min at 0°C the solution was partitioned between $NaHCO_3$ and EtOAc. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was absorbed on SiO_2 and purified by silica gel chromatography using 2% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): diastereomeric atropisomers δ 1.29 (m,

3H), 3.69 (s, 3H), 4.31 (m, 0.5H), 4.41 (m, 0.5H), 5.32 (m, 0.5H), 5.35 (m, 0.5H), 5.76 (m, 1H), 6.37 (d, 0.5H, J=2.5Hz), 6.44 (d, 0.5H, J=2.2Hz), 7.08-7.14 (m, 1H), 7.28-7.40 (m, 3H), 7.50-7.56 (m, 2H). MS(ES) 465 (M+H); LC 1: 3.63 min. and MS(ES) 465 (M+H); LC 1: 3.71min.

EXAMPLE 18

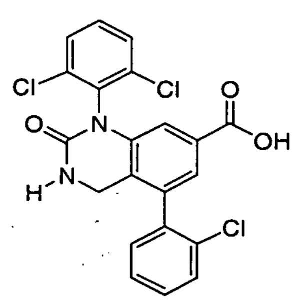
1-(2,6-dichlorophenyl)-4-methyl-5-(2-chloro-4-fluorophenyl)-7-[2-(1-piperidinyl)ethoxy]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 58**) as described in **EXAMPLE 30** and **EXAMPLE 34**. ^{1}H NMR($CDCl_3$, 500MHz): diastereomeric atropisomers δ 1.27 (m, 3H), 1.42 (m, 2H), 1.58 (m, 4H), 2.43 (brm, 4H), 2.67 (brm, 2H), 3.96 (m, 2H), 4.29 (m, 0.5H), 4.39 (m, 0.5H), 5.63 (d, 0.5H, J=3.0Hz), 5.77 (m, 1.5H), 6.37 (d, 0.5H, J=2.3Hz), 6.43 (d, 0.5H, J=2.3Hz), 7.06-7.11 (m, 1H), 7.25-7.31 (m, 1H), 7.32-7.40 (m, 2H), 7.48-7.55 (m, 2H). MS(ES) 562 (M+H); LC 1: 2.41min.

INTERMEDIATE 59

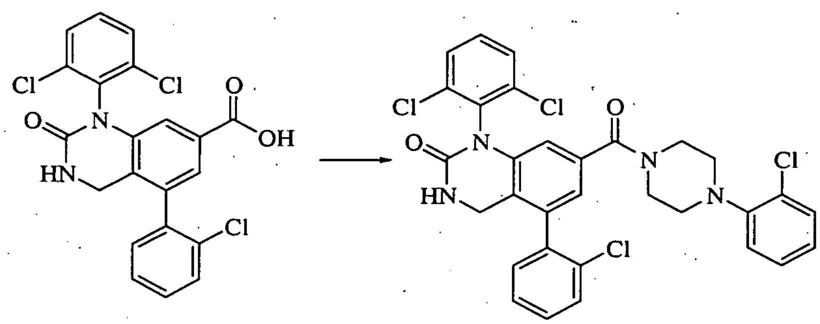
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxylate-3,4-dihydro-2(1H)-quinazolinone



To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-methylcarboxylate-3,4-dihydro-2(1H)-quinazolinone (9.6mg, 0.021 mmol) (INTERMEDIATE 32) in 1.5 mL MeOH and 0.5 mL THF was added a solution of lithium hydroxide monohydrate (129mg in 1.5mL water). After stirring overnight, 2N HCl (2mL) was added. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with brine and concentrated. The residue was purified by preparative thin layer chromatography using 20% acetone in DCM with 1% HOAc as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxylate-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR (CD_3OD): δ 4.33 (ABq, 2H, J=33.0 Hz), 6.77 (d, 1H, J=1.4 Hz), 7.32-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.49 (t, 1H, J=8.3 Hz), 7.53 (s, 2H), 7.59 (d, 1H, J=1.6 Hz), 7.60-7.62 (m, 1H). MS(ES) 447 (M+H); LC 1: 2.80min.

EXAMPLE 19

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(2-chlorophenyl)-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone

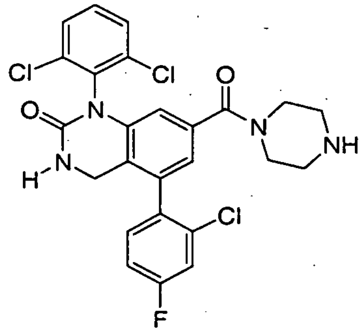


To a mixture of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (33mg, 0.17mmol) and 1-hydroxybenzotriazole hydrate (30mg, 0.22mmol) in DMF (1.3 mL) was added 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (50mg, 0.11mmol) (**INTERMEDIATE 59**). The mixture was stirred at room temperature for 15 minutes. To this was added N-(2-chlorophenyl)piperazine (33mg, 0.17mmol). The reaction mixture was then stirred at room temperature for 20 hours. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 45% acetone in hexane provided 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(2-chlorophenyl)-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone (yellow solid). ^{1}H NMR($CDCl_3$, 500MHz): δ 2.90 (brs, 2H), 3.08 (brs, 2H), 3.59 (brs, 2H), 3.89 (brm,

2H), 4.34 (d, 1H, J=14.9Hz), 4.43 (d, 1H, J=14.9Hz), 5.20 (s,1H), 6.24 (s, 1H), 6.98-7.08 (m, 3H), 7.22-7.44 (m, 6H), 7.50-7.57 (m, 3H). MS(ES) 627 (M+H); LC 1: 3.75min.

EXAMPLE 20

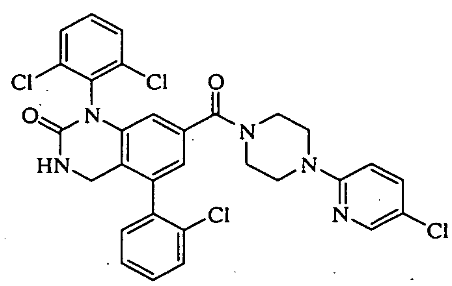
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-[N-(1-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 19** (replacing N-(2-chlorophenyl)piperazine with 1-*tert*-butoxycarbonyl-piperazine). The *tert*-butoxycarbonyl group was subsequently removed as described in **EXAMPLE 34** Step B. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 1.58-2.10 (brs, 1H), 2.63-2.87 (brm, 4H); 3.28-3.43 (brm, 2H); 3.60-3.76 (brm, 2H); 4.39 (ABq, 2H, J=13.0 Hz). MS(ES) 533 (M+H); LC 1: 1.80min.

EXAMPLE 21

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(5-chloropyridin-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone

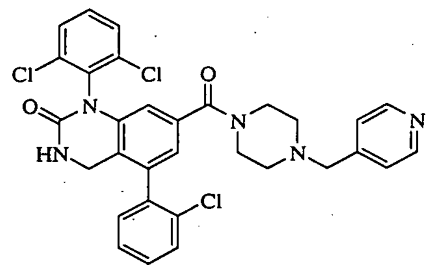


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** (replacing N-(2-chlorophenyl)piperazine with N-(5-chloropyridin-2-yl)piperazine). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.53(brs, 6H), 3.80

(brs, 2H), 4.35 (d, 1H, J=14.6Hz), 4.43 (d, 1H, J=14.8Hz), 5.11 (s,1H), 6.24 (s, 1H), 6.63 (d, 1H, J=9.1Hz), 7.00 (s, 1H), 7.30-7.43 (m, 4H), 7.48-7.57 (m, 4H), 8.16 (d, 1H, J=2.3Hz). MS(ES) 628 (M+H); LC 1: 3.36min.

EXAMPLE 22

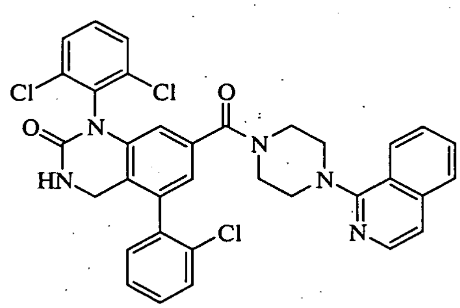
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-((pyridin-4-yl)methyl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** (replacing N-(2-chlorophenyl)piperazine with N-(pyridin-4-yl)methylpiperazine). ^{1}H NMR($CDCl_3$, 500MHz): δ 2.38(brs, 2H), 2.52 (brs, 2H), 3.45 (brs, 2H), 3.58 (s, 2H), 3.74 (brs, 2H), 4.33 (d, 1H, J=14.7Hz), 4.41 (d, 1H, J=14.7Hz), 5.11 (s,1H), 6.20 (s, 1H), 6.97 (s, 1H), 7.25-7.45 (m, 6H), 7.50-7.56 (m, 3H), 8.60 (d, 2H, J=5.0Hz). MS(ES) 608 (M+H); LC 1: 1.95min.

EXAMPLE 23

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(isoquinolin-1-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone

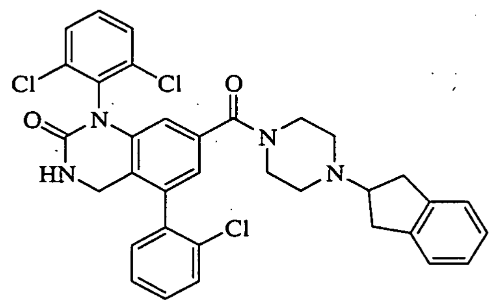


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** (replacing N-(2-chlorophenyl)piperazine with N-

(isoquinolin-1-yl)piperazine). ^{1}H NMR($CDCl_3$, 500MHz): δ 3.40(brs, 4H), 3.68 (brs, 2H), 3.95 (brs, 2H), 4.35 (d, 1H, J=14.9Hz), 4.44 (d, 1H, J=14.6Hz), 5.10 (s,1H), 6.28 (s, 1H), 7.02 (s, 1H), 7.30-7.58 (m, 9H), 7.64 (m, 1H), 7.80 (m, 1H), 8.09 (m, 1H), 8.16 (d, 1H, J=5.9Hz). MS(ES) 643 (M+H); LC 1: 2.51min.

EXAMPLE 24

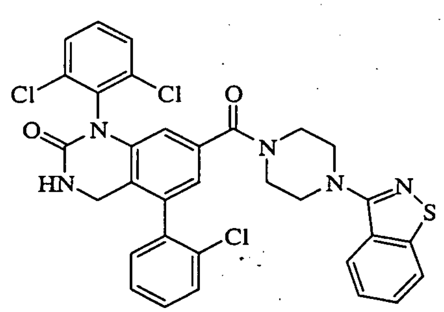
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(indan-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** (replacing N-(2-chlorophenyl)piperazine with N-(indan-2-yl)piperazine). ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 3.17(brs, 4H), 3.60 (brs, 1H), 3.80 (brm, 4H), 4.20 (brm, 4H). MS(ES) 633 (M+H); LC 1: 2.42min.

EXAMPLE 25

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(benzoisothiazol-3-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone

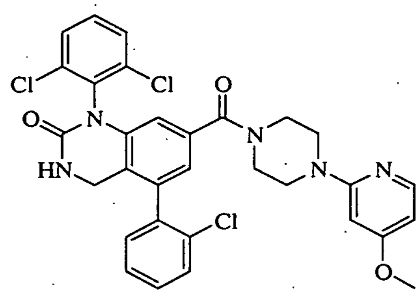


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** but replacing N-(2-chlorophenyl)piperazine with N-

(benzoisothiazol-3-yl)piperazine. [1]H NMR($CDCl_3$, 500MHz): δ 3.46(brs, 2H), 3.58 (brs, 2H), 3.66 (brs, 2H), 3.93 (brs, 2H), 4.35 (d, 1H, J=14.7Hz), 4.44 (d, 1H, J=14.9Hz), 5.16 (s,1H), 6.26 (s, 1H), 7.02 (s, 1H), 7.30-7.44 (m, 5H), 7.50-7.58 (m, 3H), 7.86 (d, 1H, J=8.0Hz), 7.92 (d, 1H, J=8.3Hz), 8.04 (s, 1H). MS(ES) 650 (M+H); LC 1: 3.73min.

EXAMPLE 26

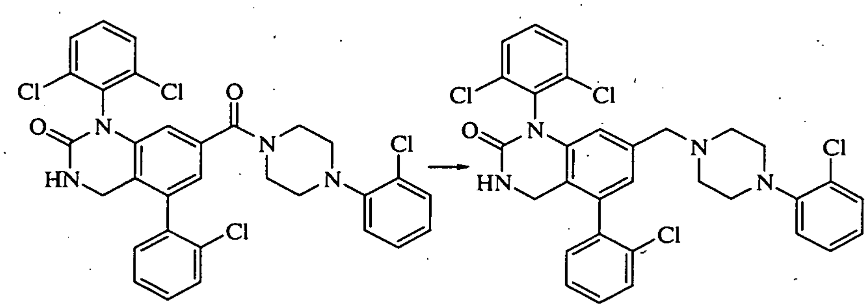
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(4-methoxypyridin-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**) as described in **EXAMPLE 19** but replacing N-(2-chlorophenyl)piperazine with N-(4-methoxypyridin-2-yl)piperazine. [1]H NMR($CDCl_3$, 500MHz): δ 3.52(brs, 6H), 3.80 (brs, 2H), 3.85 (s, 3H), 4.34 (d, 1H, J=14.9Hz), 4.44 (d, 1H, J=14.8Hz), 5.28 (s,1H), 6.11 (s, 1H), 6.23 (s, 1H), 6.33 (d, 1H, J=4.8Hz), 7.00 (s, 1H), 7.30-7.42 (m, 4H), 7.50-7.56 (m, 3H), 8.06 (d, 1H, J=5.7Hz). MS(ES) 624 (M+H); LC 1: 2.31min.

EXAMPLE 27

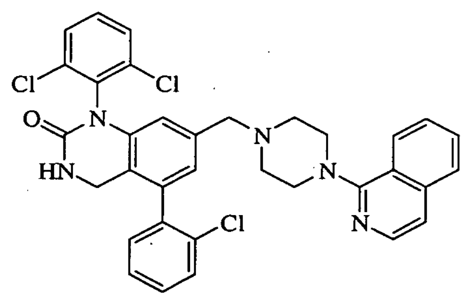
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(2-chlorophenyl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone



A solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(2-chlorophenyl)piperazinylcarbonyl]-3,4-dihydro-2 (1H) quinazolinone (**EXAMPLE 19**) (36mg, 0.0575mmol) and borane-THF complex (0.5mL of 1.0M solution, 0.5mmol) was stirred at room temperature for two hours. Methanol (1mL) was added and the mixture was stirred for 15 minutes. The solution was concentrated and the residue treated with 4.0M HCl solution in dioxane (1mL). The mixture was stirred at room temperature for two hours. The solvent was removed and neutralized with a minimum amount of 2N ammonia solution in methanol. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 50% acetone in hexanes provided 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(2-chlorophenyl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.59 (brs, 4H), 3.02 (brs, 4H), 3.49 (brs, 2H), 4.28 (d, 1H, J=14.6Hz), 4.44 (d, 1H, J=14.2Hz), 5.09 (s,1H), 6.22 (s, 1H), 6.92(s, 1H), 6.98 (t, 1H), 7.03 (d, 1H, J=7.1Hz), 7.23 (t, 1H, J=7.5Hz), 7.32-7.43 (m, 5H), 7.48-7.58 (m, 3H). MS(ES) 613 (M+H); LC 1: 2.73min.

EXAMPLE 28

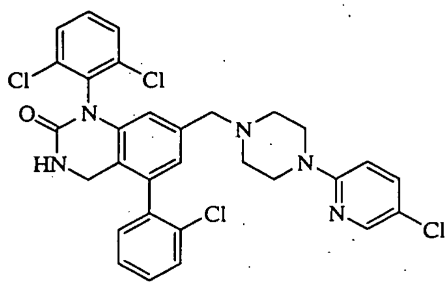
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)- 7-[N-(isoquinolin-1-yl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(isoquinolin-1-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 23**) similarly to that procedure described in **EXAMPLE 27**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.68 (brs, 4H), 3.39 (brs, 4H), 3.55 (brs, 2H), 4.28 (d, 1H, J=14.5Hz), 4.44 (d, 1H, J=14.4Hz), 5.16 (s,1H), 6.25 (s, 1H), 6.94 (s, 1H), 7.25 (d, 1H, J=6.0Hz), 7.30-7.42 (m, 4H), 7.47-7.57 (m, 4H), 7.62 (t, 1H, J=7.5Hz), 7.76 (d, 1H, J=8.0Hz), 8.07 (d, 1H, J=8.5Hz), 8.15 (d, 1H, J=5.8Hz). MS(ES) 630 (M+H); LC 1: 2.35min.

EXAMPLE 29

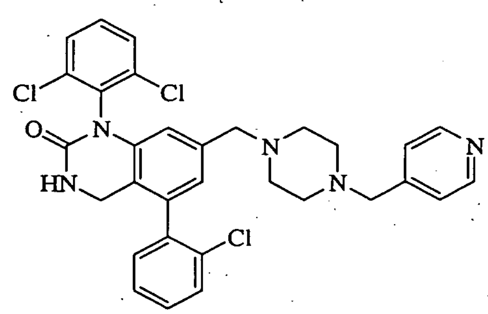
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(5-chloropyridin-2-yl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(5-chloropyridin-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 21**) as described in **EXAMPLE 27**. MS(ES) 614 (M+H); LC 1: 2.68min.

EXAMPLE 30

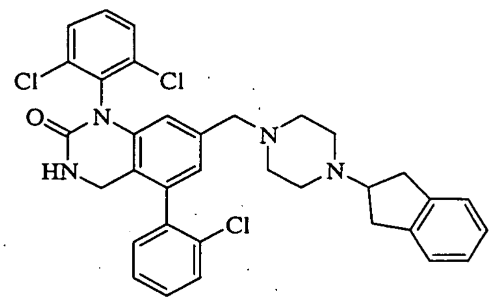
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-((pyridin-4-yl)methyl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-((pyridin-4-yl)methyl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 22**) as described in **EXAMPLE 27**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.44 (brs, 8H), 3.43 (brs, 2H), 3.51 (s, 2H), 4.26 (d, 1H, J=14.6Hz), 4.42 (d, 1H, J=14.2Hz), 5.12 (s,1H), 6.16 (s, 1H), 6.88 (s, 1H), 7.22-7.57 (m, 9H), 8.55 (d, 2H, J=5.3Hz). MS MS(ES) 594 (M+H); LC 1: 1.84min.

EXAMPLE 31

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(indan-2-yl)piperazinylmethyl]-3,4-dihydro-2(1H)-quinazolinone

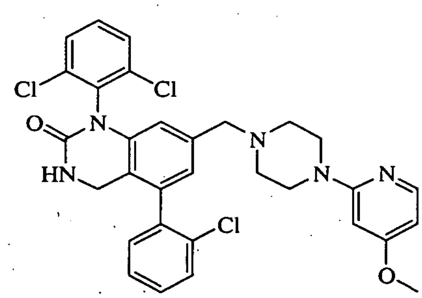


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(indan-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)quinazolinone (**EXAMPLE 24**) as described in **EXAMPLE 27**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.55 (brs, 8H), 2.96 (brs, 2H), 3.10 (brs, 2H), 3.22 (brs, 2H), 3.45 (s, 2H), 4.26 (d, 1H, J=14.4Hz), 4.43 (d, 1H, J=14.4Hz), 5.09 (s,1H), 6.16 (s, 1H), 6.88 (s, 1H), 7.13-7.22 (m, 4H), 7.30-7.43 (m, 4H), 7.48-7.57 (m, 3H).

MS(ES) 619 (M+H); LC 1: 2.61min.

EXAMPLE 32

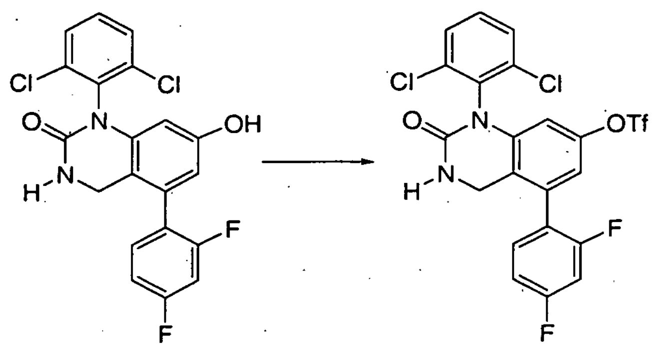
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(4-methoxypyridin-2-yl)piperazinylmethyl] -3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-(4-methoxypyridin-2-yl)piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone. (**EXAMPLE 26**) as described in **EXAMPLE 27**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.51 (brs, 4H), 3.48 (brs, 6H), 3.83 (s, 3H), 4.27 (d, 1H, J=14.1Hz), 4.44 (d, 1H, J=14.5Hz), 5.13 (s,1H), 6.09 (s, 1H), 6.22 (s, 1H), 6.28 (d, 1H, J=5.3Hz), 6.90 (s, 1H), 7.30-7.42 (m, 4H), 7.48-7.57 (m, 3H), 8.05 (d, 1H, J=5.9Hz). MS(ES) 610 (M+H); LC 1: 1.9min.

INTERMEDIATE 60

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone



Solid 2-[N,N-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (60mg, 0.20mmol) was added to 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (64mg, 0.152mmol) (**INTERMEDIATE 48**) in 2mL THF. After 1h the solution was partitioned between EtOAc and $NaHCO_3$. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography using 3% acetone in DCM to give 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 4.25-4.54 (brm, 2H), 5.75 (s, 1H), 6.05 (d, 1H, J=2.3Hz), 6.89 (d, 1H, J=2.3Hz), 6.95-7.07 (m, 2H), 7.22-7.37 (m, 1H), 7.43 (t, 1H, J=7.7Hz), 7.56 (d, 2H, J=8.0Hz). MS(ES) 553 (M+H); LC 1: 4.03min.

INTERMEDIATE 61

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 49**) as described in **INTERMEDIATE 60**. ^{1}H NMR($CDCl_3$, 500MHz): δ 4.27 (dd, 1H, J=14.9, 1.6Hz), 4.41 (dd, 1H, J=14.8, 1.3Hz), 5.38 (s, 1H), 6.03 (d, 1H, J=2.3Hz), 6.84 (d, 1H, J=2.3Hz), 7.28-7.31 (m, 3H), 7.35-7.44 (m, 3H), 7.51-7.57 (m, 3H). MS(ES) 551 (M+H); LC 1: 3.47min.

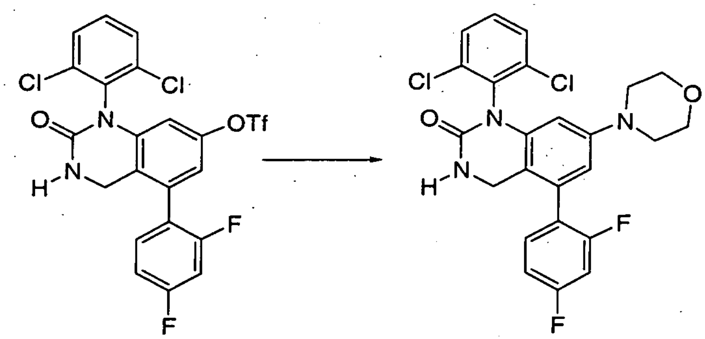
INTERMEDIATE 62

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone

The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-hydroxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 50**) as described in **INTERMEDIATE 60**. MS(ES) 569 (M+H); LC 1: 3.51min.

EXAMPLE 33

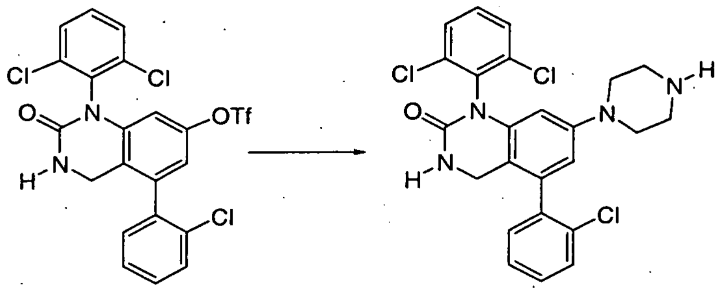
1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1-morpholinyl)-3,4-dihydro-2(1H)-quinazolinone



To dry Cs_2CO_3 (46mg, 0.141mmol) under argon was added $Pd(OAc)_2$ (6mg, 0.027mmol), racemic BINAP (25mg, 0.04mmol) and 1.2mL anhydrous 1,4-dioxane. To the orange suspension was added morpholine (0.09mL, 1.02mmol) and 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-oxytrifluormethylsulfonyl-3,4-dihydro-2(1H)-quinazolinone (19mg, 0.034mmol) (**INTERMEDIATE 60**). The solution was then heated at 96°C for 2 hours under an argon atmosphere. The solution was cooled to RT and partitioned between saturated $NaHCO_3$ (5mL) and EtOAc (15mL). The organic phase was washed with brine and dried over $MgSO_4$. The solution was filtered through a small plug of silica gel and concentrated. The residue was purified by thin layer chromatography using ethyl ether as the eluent to give 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1-morpholinyl)-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): δ 2.98 (t, 4H, J=4.8Hz), 3.77 (t, 4H, J=4.8Hz), 4.20-4.50 (br m, 2H), 5.31 (s, 1H), 5.69 (d, 1H, J=2.2Hz), 6.47 (d, 1H, J=2.5Hz), 6.90-7.00 (m, 2H), 7.23-7.31 (m, 1H), 7.38 (t, 1H, J=8.1Hz), 7.54 (d, 2H, J=8.0Hz). MS(ES) 490 (M+H); LC 1: 3.12min.

EXAMPLE 34

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1-piperazinyl)-3,4-dihydro-2(1H)-quinazolinone



Step A: 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(N-Boc-piperazinyl)-3,4-dihydro-2(1H)-quinazolinone

To dry Cs_2CO_3 (130mg, 0.399mmol) under argon was added $Pd(OAc)_2$ (6.5mg, 0.029mmol), racemic BINAP (35mg, 0.056mmol), 1-*tert*-butoxycarbonyl-piperazine (60mg, 0.32mmol) and 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (54mg, 0.098mmol) (**INTERMEDIATE 61**) in 2mL 1,4-dioxane. The solution was then heated at 100°C for 8hrs under an argon atmosphere. The solution was cooled to RT and partition between $NaHCO_3$ and ethyl ether. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was absorbed on SiO_2 and purified by silica gel chromatography using 1 to 5% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(N-Boc-piperazinyl)-3,4-dihydro-2(1H)-quinazolinone. MS(ES) 587 (M+H), 531 (M-tBu+2H); LC 1: 4.04min.

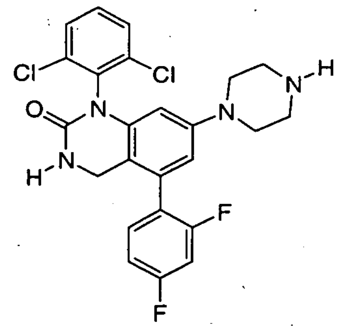
Step B:

To 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(N-Boc-piperazinyl)-3,4-dihydro-2(1H)-quinazolinone (34mg, 0.058mmol) was added anisole (0.4mL) and 1/1 TFA/DCM (5mL). After 2h the solution was concentrated and the residue partition between EtOAc and 1N NaOH (saturated with NaCl). The phases were separated and the organic phase dried over Na_2SO_4, filtered and concentrated. The residue was purified by thin layer chromatography using EtOAC followed by $CHCl_3$/MeOH/NH_4OH (87/12/1) as the eluent to give 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1-piperazinyl)-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): δ 1.80 (brs, 1H, NH), 2.89-3.00 (m, 8H), 4.17 (d, 1H, J=13.9Hz), 4.36 (d, 1H, 13.8Hz), 5.28 (s, 1H), 5.69 (d, 1H, J=2.0Hz), 6.45 (d, 1H,

J=2.2Hz), 7.30-7.40 (m, 4H), 7.47-7.51 (m, 1H), 7.53 (d, 2H, J=8.2Hz). MS(ES) 487 (M+H); LC 1: 2.04min.

EXAMPLE 35

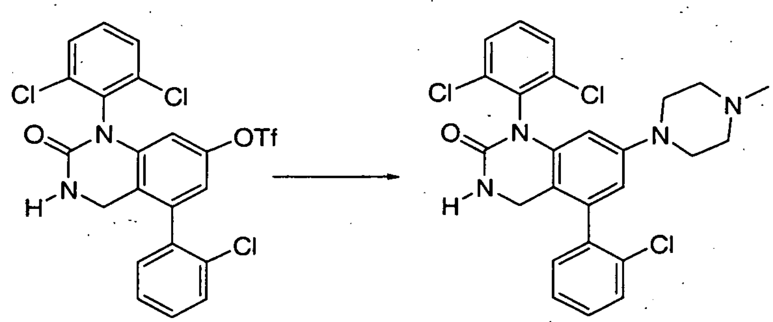
1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-piperazinyl-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 60**) as described in **EXAMPLE 34**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.89-3.0 (m, 8H), 4.20-4.50 (br m, 2H), 5.16 (s, 1H), 5.72 (d, 1H, J=2.3Hz), 6.48 (d, 1H, J=2.3Hz), 6.90-7.01 (m, 1H), 7.25-7.32 (m, 1H), 7.38 (app t, 1H, J=8Hz), 7.53 (d, 2H, J=8.2Hz). MS(ES) 489 (M+H); LC 1: 2.00min.

EXAMPLE 36

1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-(4-methyl)piperazinyl-3,4-dihydro-2(1H)-quinazolinone

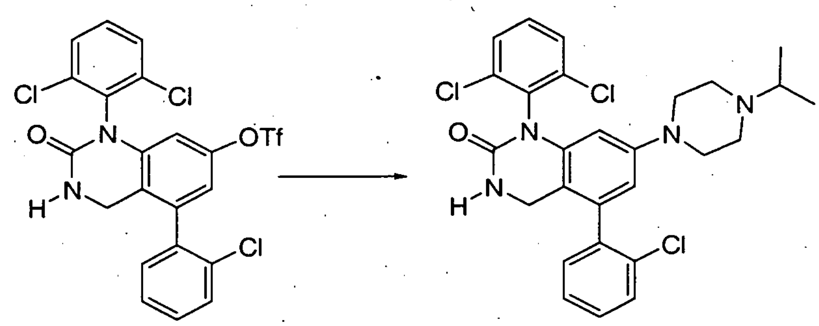


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone

(**INTERMEDIATE 61**) and 4-methylpiperazine as described in **EXAMPLE 33**. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 2.41 (s, 3H), 2.64 (brs, 4H), 3.11 (m, 4H). MS(ES) 501 (M+H); LC 1: 1.98 min.

EXAMPLE 37

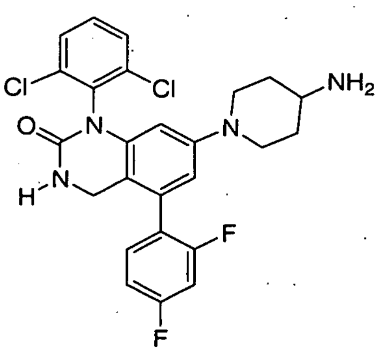
<u>1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-[4-(2-propyl)piperazinyl]-3,4-dihydro-2(1H)-quinazolinone</u>



1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-[4-(2-propyl)piperazinyl]-3,4-dihydro-2(1H)-quinazolinone was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) and 4-isopropylpiperazine as described in **EXAMPLE 33**. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.03 (d, J = 6.6 Hz, 6H), 2.58 (m, 4H), 2.65 (m, 1H), 3.0 (m, 4H). MS(ES) 529 (M+H); LC 1: 2.24 min.

EXAMPLE 38

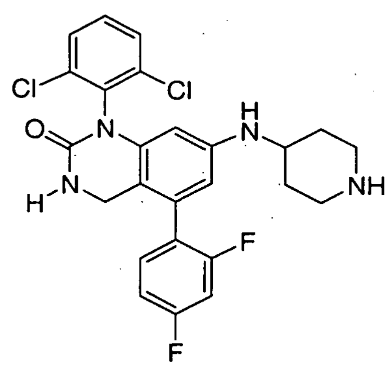
<u>1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(4-amino-1-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 60**) as described in **EXAMPLE 34** (replacing 1-Boc-piperazine with 4-Boc-amino-1-piperidine). ^{1}H NMR($CDCl_3$, 500MHz): δ 1.34-1.46 (brm, 2H), 1.80-1.86 (brm, 2H), 2.67 (app t, 2H, J=11.9Hz), 2.79 (brm, 1H), 3.36-3.43 (m, 2H), 4.20-4.45 (brm, 2H), 5.18 (s, 1H), 5.72 (s, 1H), 6.50 (s, 1H), 6.89-7.00 (m, 2H), 7.29-7.31 (m, 1H), 7.38(t, 1H, J=7.9Hz), 7.53 (d, 2H, J=8.0Hz). MS(ES) 503 (M+H); LC 1: 2.03min.

EXAMPLE 39

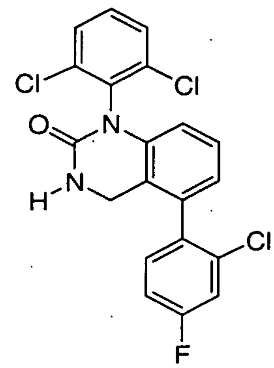
<u>1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(amino(N-4-piperidinyl))-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 60**) as described in **EXAMPLE 34** (replacing 1-Boc-piperazine with 4-amino-1-Boc-piperidine). ^{1}H NMR($CDCl_3$, 500MHz): δ 1.30-1.41 (brm, 2H), 2.02 (brm, 2H), 2.67 (brm, 2H), 3.17 (brm, 2H), 3.52 (brm, 1H), 4.15-4.42 (brm, 2H), 5.22 (s, 1H), 5.36 (d, 1H, J=2.3Hz), 6.16 (d, 1H, J=2.3Hz), 6.90-7.00 (m, 2H), 7.25-7.31 (m, 1H), 7.38 (t, 1H, J=8.1Hz), 7.53 (d, 2H, J=8.0Hz). MS(ES) 503 (M+H), 420 (M-piperidine+2H); LC 1: 2.31 min.

INTERMEDIATE 63

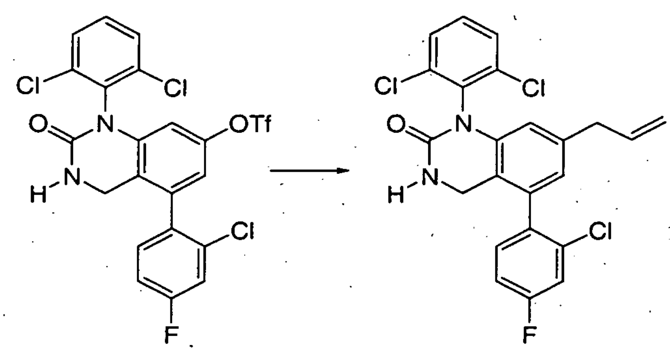
<u>1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 62**) and was isolated as a minor component in the preparation of **EXAMPLE 43**. ^{1}H NMR($CDCl_3$, 500MHz): δ 4.27 (dd, 1H, J=14.4, 1.7Hz), 4.43 (dd, 1H, J=14.5, 1.2Hz), 5.30 (s, 1H), 6.19 (d, 1H, J=8.2Hz), 6.88 (d, 1H, J=7.6Hz), 7.09 (app dt, 1H, J=8.2, 2.5Hz), 7.17 (t, 1H, J= 8.0Hz), 7.25-7.31 (m, 2H), 7.38 (t, 1H, J=8.0Hz), 7.53 (d, 2H, J=8.2Hz). MS(ES) 421 (M+H); LC 1: 4.37 min.

INTERMEDIATE 64

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-allyl-3,4-dihydro-2(1H)-quinazolinone

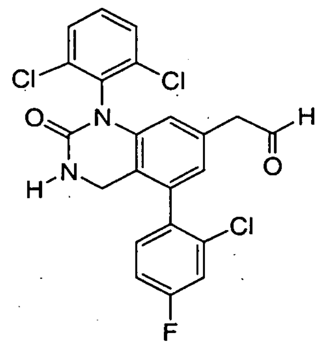


To dry lithium chloride (23.1mg, 0.546mmol) was added 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (29.6mg, 0.052mmol) (**INTERMEDIATE 62**), 2mL anhydrous 1,4-dioxane, allyltri-n-butyl tin (52.1mg, 0.157mmol) and palladium tetrakis triphenyl phosphine (8.3mg, 0.0072mmol). The solution was then reflux under an argon atmosphere. After 4 hours the solution was cooled to RT, diluted with ethyl acetate, filtered through Celite and concentrated. The residue was purified by preparative thin

layer chromatography using 5% acetone in methylene chloride as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-allyl-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 3.26 (d, 2H, J=6.4 Hz), 5.00 (dd, 1H, J=27.7and 1.5 Hz); 5.01 (s, 1H); 5.86-5.98 (m, 1H). MS(ES) 461 (M+H); LC 1: 3.84 min.

INTERMEDIATE 65

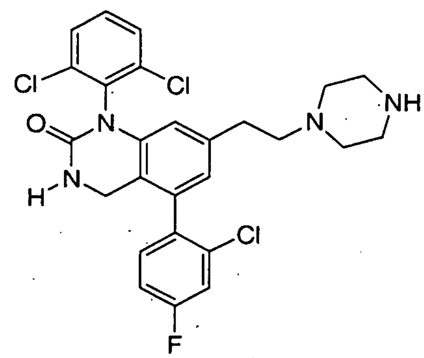
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-acetylaldehyde-3,4-dihydro-2(1H)-quinazolinone



1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-allyl-3,4-dihydro-2(1H)-quinazolinone (15mg, 0.032 mmol) (**INTERMEDIATE 64**) in 0.5 mL THF was added $NaIO_4$ (26.3mg, 0.123mmol) in 0.3 mL water followed by catalytic amount of OsO4. After stirring at room temperature overnight the solution was partitioned between EtOAc and water. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative thin layer chromatography using 5% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-acetylaldehyde-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 3.49 (s, 2H); 9.57 (s, 1H). MS(ES) 463 (M+H); LC 1: 2.98min.

EXAMPLE 40

1-(2,6-dichlorophenyl)-5-(2-chloro-4-difluorophenyl)-7-[ethyl-2-(1-piperazinyl)]-3,4-dihydro-2(1H)-quinazolinone



Step A: 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(N-Boc-piperazinylethyl)-3,4-dihydro-2(1H)-quinazolinone

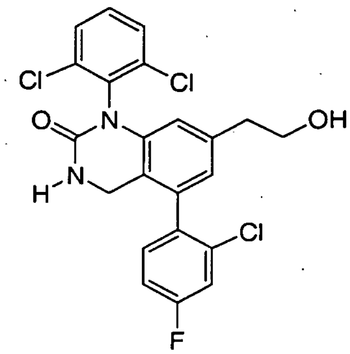
To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-acetylaldehyde-3,4-dihydro-2(1H)-quinazolinone (4.3mg, 0.0093mmol) (**INTERMEDIATE 65**) in 1.0mL methanol was added 1-Boc-piperazine (7.5mg, 0.040mmol) and sodium cyanoborohydide (95mg, 0.15mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was partition between water and ethyl acetate. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative thin layer chromatography using 6% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(N-Boc-piperazinylethyl)-3,4-dihydro-2(1H)-quinazolinone. MS(ES) 633 (M+H); LC 1: 2.64min.

Step B: 1-(2,6-dichlorophenyl)-5-(2-chloro-4-difluorophenyl)-7-[ethyl-2-(1-piperazinyl)]-3,4-dihydro-2(1H)-quinazolinone

To 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(N-Boc-piperazinylethyl)-3,4-dihydro-2(1H)-quinazolinone (1.7mg, 0.0027mmol) was added 1/1 TFA/DCM (0.5mL). After 2hours the solution was concentrated and the residue partition between EtOAc and water. The phases were separated and the organic phase was concentrated. The residue was purified by thin layer chromatography using $CHCl_3$/MeOH/NH_4OH (87/12/1) as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-difluorophenyl)-7-[ethyl-2-(1-piperazinyl)]-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): selected data δ 2.41 (brs, 4H); 2.49 (t, 2H, J=7.8 Hz); 2.67 (t, 2H, J=7.4 Hz); 2.86 (t, 4H, J=4.8 Hz). MS(ES) 533 (M+H); LC 1: 1.89min.

INTERMEDIATE 66

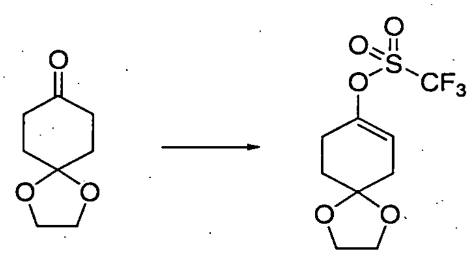
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-acetylaldehyde-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-acetylaldehyde-3,4-dihydro-2(1H)-quinazolinone (4.3mg, 0.0093mmol) (**INTERMEDIATE 65**) was isolated as a minor component in **EXAMPLE 40**. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 2.74 (t, 2H, J=6.5HZ), 3.77 (m, 2H). MS(ES) 465 (M+H); LC 1: 2.79min.

INTERMEDIATE 67

(1,4-Dioxaspiro(4.5)dec-7-ene-8-yl)trifluoromethylsulfurate

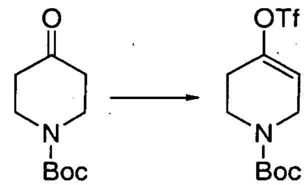


To a solution of 1,4-cyclohexanedione mono-ethylene ketal (1.35 g, 8.64 mmol) in THF (15 mL) at 78°C was added lithium bis(trimethylsilyl)amide (12.1 mL, 1.0M in THF) dropwise. The mixture was stirred for 30 minutes at -78°C then warmed to 0°C for 30 minutes. It was cooled down to –78°C again then added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (4.75g, 12.1mmol) dissolved in THF (10 mL) rapidly. The reaction mixture was stirred while the bath temperature was warming to –40°C over 4h. The reaction was quenched with saturated $NaHCO_3$ solution and removed the solvent in vacuo. It was extracted three times with EtOAc, the combined extracts were washed with brine, and it was dried over Na_2SO_4. After removal of solvent, the crude material was purified by flash

chromatography eluting with 1:10 EtOAc:hexanes to obtain (1,4-Dioxaspiro(4.5)dec-7-ene-8-yl)trifluoromethylsulfurate. ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.9 (t, 2H, J = 6.6 Hz), 2.4 (m, 2H), 2.53 (m, 4H), 3.98 (m, 4H), 5.65 (m, 1H).

INTERMEDIATE 68

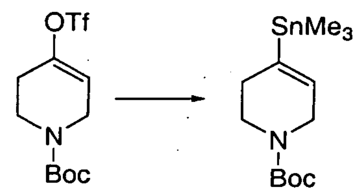
4-trifluoromethylsulfonato-1-Boc-1,2,3,6-tetrahydro-pyridine



The title compound was prepared from 1-Boc-4-piperidone as described in **INTERMEDIATE 67**. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.49 (s, 1H), 2.46 (brs, 2H), 3.65 (brs, 2H), 4.06 (brs, 2H), 5.78 (s, 1H).

INTERMEDIATE 69

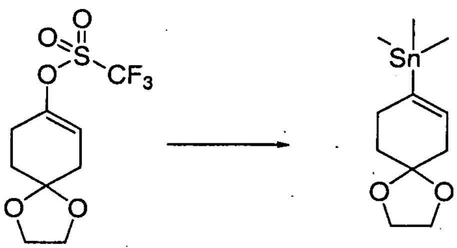
4-trimethyltin-1-Boc-1,2,3,6-tetrahydro–pyridine



To 4-trifluoromethylsulfonate-1-Boc 1,2,3,6-tetrahydro–pyridine (189mg, 0.57mmol) (**INTERMEDIATE 68**) and hexamethylditin (220mg, 0.67mmol) in THF (2mL) under an argon atmosphere was added LiCl (95mg, 2.24mmol) and palladium tetrakis triphenyl phosphine (15mg, 0.013mmol). After refluxing overnight the solution was concentrated and the residue partitioned between water and ethyl ether. The phases were separated and the organic washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography using 5 to 10% ethyl ether in hexanes (with 1% triethylamine) as the eluent to give 4-trimethyltin-1-Boc-1,2,3,6-tetrahydro–pyridine. ^{1}H NMR($CDCl_3$, 500MHz): δ 0.11 (s, 6H), 1.46 (s, 9H), 2.26 (brs, 2H), 3.46 (m, 2H), 3.90 (brs, 2H), 5.75 (brs, 1H). LC 1: 4.37 min.

INTERMEDIATE 70

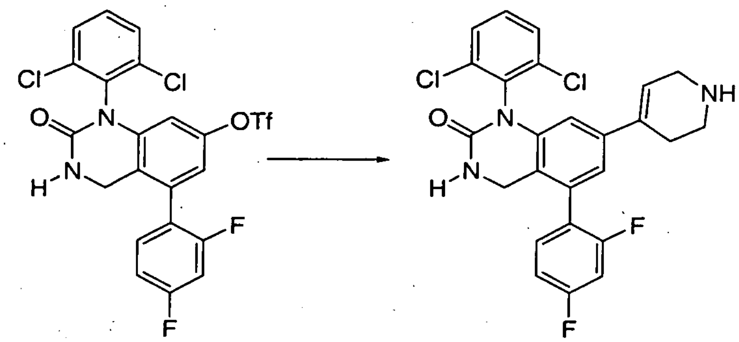
(1,4-Dioxaspiro(4.5)dec-7-ene-8-yl)trimethyl tin



The title compound was prepared according to the procedure found in Wulff, W. D.; et. al.; *J. Org. Chem.*, **1986**, 51, 277. ^{1}H NMR ($CDCl_3$, 500MHz): δ 0.1 (s, 9H), 1.75 (t, 2H, J = 6.4 Hz), 2.34 (m, 2H), 2.41 (m, 4H), 3.98 (m, 4H), 5.74 (m, 1H).

EXAMPLE 41

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone



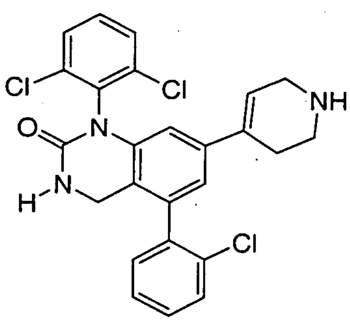
Step A: To dry lithium chloride (43mg, 1.01mmol) was added 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (167mg, 0.302mmol) (**INTERMEDIATE 60**), 6mL anhydrous 1,4-dioxane, 4-trimethyltin-1-Boc-1,2,3,6-tetrahydro–pyridine (250mg, 0.724mmol) (**INTERMEDIATE 69**) and palladium tetrakis triphenyl phosphine (58mg, 0.05mmol). The solution was then heated at 100°C under an argon atmosphere. After 24 hours the solution was cooled to RT, diluted with ethyl ether, filtered through Celite and concentrated. The residue was purified by silica gel chromatography using 3% to 8% acetone in DCM as the eluent to give 160mg of product (90% yield). ^{1}H NMR($CDCl_3$, 500MHz): δ 1.47 (s,9H), 2.34 (brs, 2H), 3.56 (brs, 2H), 4.00 (brs, 2H), 4.28-4.57 (brm, 2H), 5.14 (s, 1H), 5.85 (brs, 1H), 6.15 (s, 1H), 6.95 (s, 1H), 6.96-7.00

(m, 2H), 7.29-7.32 (m,1 H), 7.41 (t, 1H, 8.0Hz), 7.55 (d, 2H, J=8.3Hz). MS(ES) 586 (M+H); LC 1: 3.97min.

Step B: The *tert*-butoxycarbonyl substituent was removed as described in **EXAMPLE 34,** Step B. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.30 (brm, 2H), 3.05 (t, 2H, J=5.8Hz), 3.48 (d, 2H, J=3.0Hz), 4.24-4.58(brm, 4H), 5.18 (s, 1H), 5.92 (brs, 1H), 6.16 (t, 1H, J=7.8Hz), 7.55 (d, 2H, J=8.0Hz). MS(ES) 486 (M+H); LC 1: 1.99min.

EXAMPLE 42

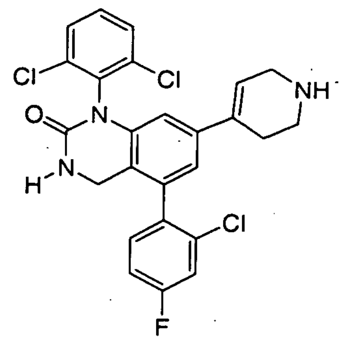
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) as described in **EXAMPLE 41**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.15 (brm, 1H, NH), 2.28 (brm, 2H), 3.03 (t, 2H, J=5.7Hz), 4.24 (d, 1H, 14.7Hz), 4.42 (d, 1H, J=14.7Hz), 5.56 (s, 1H), 5.93 (s, 1H), 6.13 (d, 1H, J=1.4Hz), 6.91 (d, 1H, J=1.4Hz), 7.28-7.40 (m, 4H), 7.48-7.56 (m, 3H). MS(ES) 484 (M+H); LC 1: 2.10 min.

EXAMPLE 43

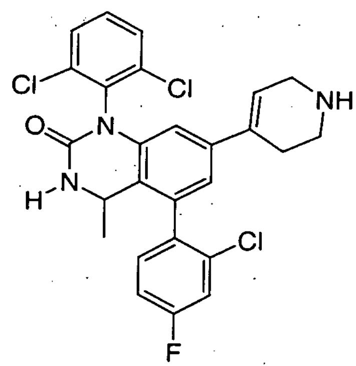
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 62**) as described in **EXAMPLE 41**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.42 (brs, 2H), 3.14 (t, 2h, J=5.7Hz), 3.57 (m, 2H), 4.25 (app dd, 1H, J=1.6, 14.7Hz), 4.42 (app dd, 1H, J=1.7, 14.6Hz), 5.14 (s, 1H), 5.90 (s, 1H), 6.14 (d, 1H, J=1.4Hz), 6.88 (d, 1H, J=1.6Hz), 7.08-7.12 (m, 1H), 7.26-7.32 (m, 2H), 7.40 (t, 1H, J=8.0Hz), 7.55 (d, 2H, J=8.2Hz). MS(ES) 502 (M+H); LC 1: 2.06min.

EXAMPLE 44

1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone

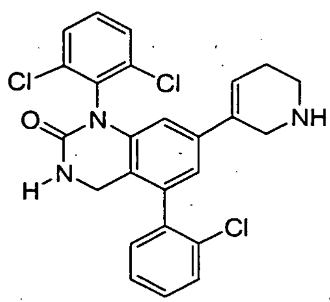


The title compound was prepared from 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone as described in **EXAMPLE 41**. 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone was prepared from 1-(2,6-dichlorophenyl)-3-methyl-5-(2-chloro-4-fluorophenyl)-7-methoxy-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 58**) as described in **INTERMEDIATE 48** and **INTERMEDIATE 60**. ^{1}H NMR($CDCl_3$, 500MHz):

diastereomeric atropisomers δ 1.32 (m, 3H), 2.37 (brs, 2H), 2.51 (brm, 1H), 3.10 (t, 2H, J=5.7Hz), 3.53 (brs, 2H), 4.36 (m, 0.5H), 4.47 (m, 0.5H), 5.51 (d, 0.5H, 2.9Hz), 5.58 (d, 0.5H, J=2.7Hz), 5.90 (brs, 1H), 6.13 (s, 0.5H), 6.15 (s, 0.5H), 6.83 (s, 0.5H), 6.90 (s, 0.5H), 7.09-7.13 (m, 1H), 7.28-7.42 (m, 3H), 7.51-7.58 (m, 2H). MS(ES) 516 (M+H); LC 1: 2.22min.

EXAMPLE 45

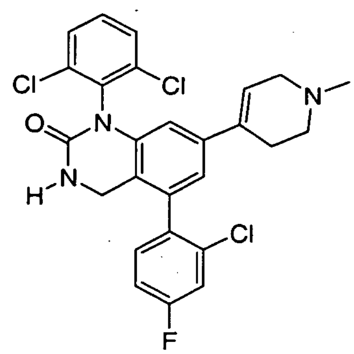
<u>1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1,2,3,6-tetrahydro-5-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) and 5-trimethyltin-1-Boc-1,2,3,6-tetrahydro–pyridine as described in **EXAMPLE 41**. 5-Trimethyltin-1-Boc-1,2,3,6-tetrahydro–pyridine was prepared as described in **INTERMEDIATE 68** and **INTERMEDIATE 69** replacing 1-Boc-4-piperidone with 1-Boc-3-piperidone. ^{1}H NMR(CD_3OD, 500MHz): δ 2.15-2.22 (m, 2H), 2.87 (t, 2H, J=5.9Hz), 3.44 (m, 2H), 4.21 (d, 1H, J=15.1Hz), 4.29 (d, 1H, J=15.1Hz), 5.97 (m, 1H), 6.05 (d, 1H, 1.6Hz), 6.86 (d, 1H, J=1.4Hz), 7.31-7.35 (m, 1H), 7.40-7.44 (m, 2H), 7.47-7.56 (m, 2H), 7.61-7.64 (m, 2H). MS(ES) 525 (M+ CH_3CN+H), 484 (M+H); LC 1: 2.15 min.

EXAMPLE 46

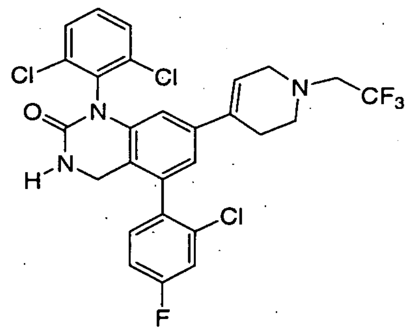
<u>1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 43**) as described in **EXAMPLE 15**. ^{1}H NMR($CDCl_3$, 500MHz): δ 2.37 (s, 3H), 2.39 (brm, 2H) 2.59 (t, 2H, J=5.8Hz), 3.00 (m, 2H), 4.23 (app dd, 1H, J=1.7, 14.5Hz), 4.39 (app dd, 1H, J=1.4, 14.6Hz), 5.34 (s, 1H), 5.85 (m, 1H), 6.14 (d, 1H, J=1.4Hz), 6.87 (d, 1H, J=1.6Hz), 7.06-7.10 (m, 1H), 7.24-7.31 (m, 2H), 7.38 (t, 1H, J=8.0Hz), 7.53 (d, 2H, J=7.8Hz). MS(ES) 516 (M+H); LC 1: 2.13min.

EXAMPLE 47

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone

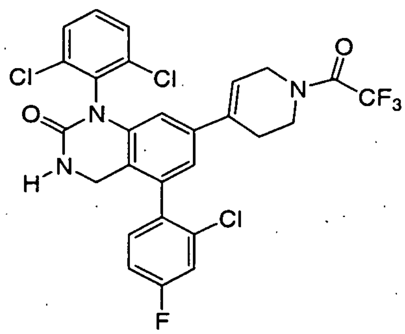


To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-(1,2,3,6-tetrahydro-5-pyridinyl-l-3,4-dihydro-2(1H)-quinazolinone (13.1mg, 0.026mmol) (**EXAMPLE 43**) in 0.5mL dichloromethane was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (33.9mg, 0.146mmol) followed by N,N-diisopropylethylamine (37.1mg, 0.288mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with brine and

concentrated. The residue was purified by preparative thin layer chromatography using 5% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ: 2.40 (d, 2H, J=1.8 Hz); 2.87 (t. 2H, J=5.7 Hz); 3.07 (q, 2H, J=9.6 Hz); 3.33 (d, 2H, J=3.0 Hz). MS(ES) 584 (M+H); LC 1: 3.25 min.

EXAMPLE 48

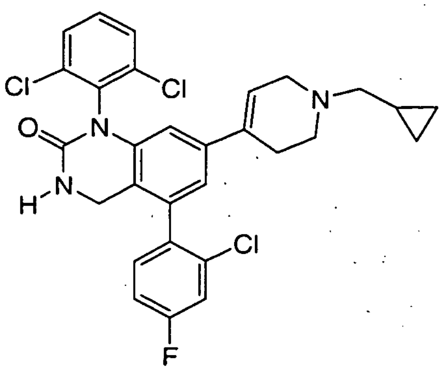
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(trifluoracetyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone



To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-(1,2,3,6-tetrahydro-5-pyridinyl-l-3,4-dihydro-2(1H)-quinazolinone (4.6mg, 0.0091mmol) (**EXAMPLE 43**) in 0.25mL dichloromethane was added trifluoroacetic anhydride (15mg, 0.71mmol) followed by N,N-diisopropylethylamine (37.1mg, 0.288mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with brine and concentrated. The residue was purified by preparative thin layer chromatography using 5% acetone in DCM as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(trifluoracetyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 2.48 (brm, 2H); 3.75 (t, 1H, J=5.8 Hz); 3.79-3.87 (m, 1H); 4.19-4.25 (m, 2H); 5.89 (m, 1H). MS(ES) 598 (M+H), LC 1: 3.65min.

EXAMPLE 49

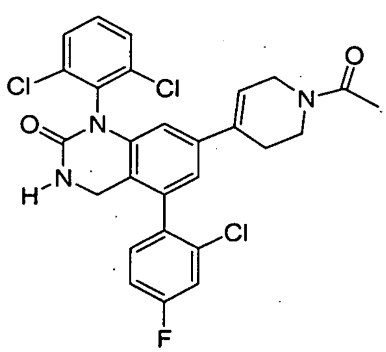
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(methylcyclopropyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone



To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl-4-fluoro)-7-(1,2,3,6-tetrahydro-5-pyridinyl-l-3,4-dihydro-2(1H)-quinazolinone (14.8mg, 0.0294mmol) (**EXAMPLE 43**) in 1mL ethanol was added (bromomethyl)-cyclopropane (20.6mg, 0.153mmol) followed by triethylamine (25mg, 0.24mmol). The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with brine and concentrated. The residue was purified by preparative thin layer chromatography using 4% methanol in ethyl acetate to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(methylcyclopropyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 0.17 (d, 2H, J=4.1 Hz); 0.81-0.86 (m, 1H); 0.56 (d, 2H, J=7.6 Hz); 2.40 (s, 2H); 2.45 (s, 2H); 2.77 (s, 2H); 3.23 (s, 2H); 5.88 (s, 1H). MS(ES) 556 (M+H), LC 1: 2.53min.

EXAMPLE 50

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1,2,3,6-tetrahydro-1-(acetyl)-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone

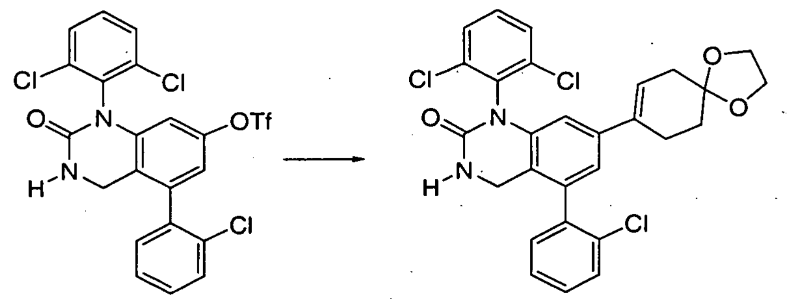


The title compound was prepared as described in **EXAMPLE 48** (replacing trifluoroacetic anhydride with acetic anhydride). ^{1}H NMR($CDCl_3$,

500MHz): selected data δ: 2.38 (d, 2H, J=31.1 Hz); 3.59 (t, 1H, J=5.7 Hz); 3.68-3.79 (m, 1H); 4.06 (d, 1H, J=2.8 Hz); 4.16 (d, 1H, J=2.8 Hz); 5.88 (d, 1H, J=20.4 Hz). MS(ES) 544 (M+H), LC 1: 3.06min.

INTERMEDIATE 71

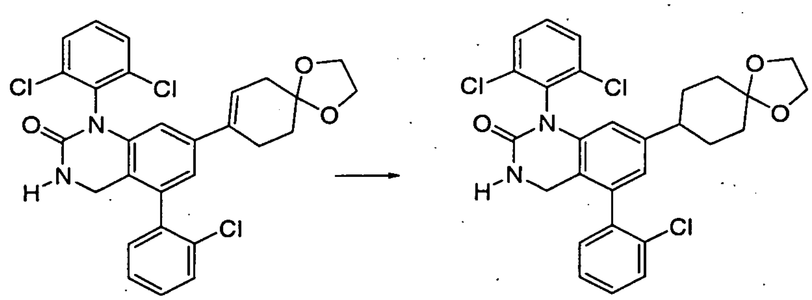
1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-7-ene-8-yl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) and (1,4-Dioxaspiro(4.5)dec-7-ene-8-yl)trimethyl tin (**INTERMEDIATE 70**) as described in **EXAMPLE 41**. ^{1}H NMR (CDCl$_3$, 500MHz): selected data δ 1.82 (t, 2H, J = 6.4 Hz), 2.38 (brs, 2H), 2.47 (m, 2H), 3.97 (s, 4H), 5.83 (t, 1H, J = 3.9 Hz). MS(ES) 541 (M+H); LC 1: 3.64 min.

INTERMEDIATE 72

1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone

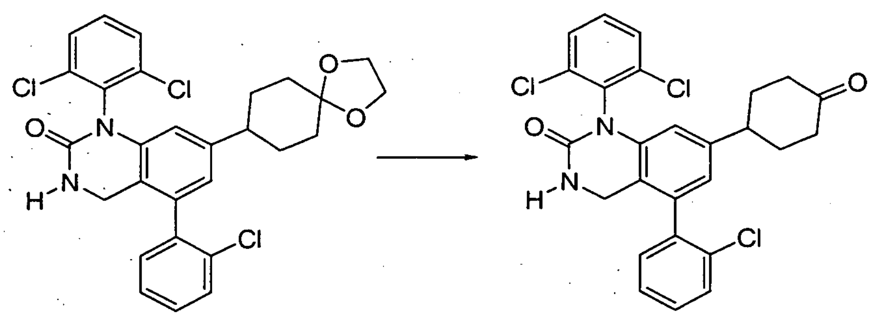


To 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-7-ene-8-yl)-3,4-dihydro-2(1H)-quinazolinone (818.8mg, 1.51 mmol) (**INTERMEDIATE 71**) in ethyl acetate (25mL) under a nitrogen atmosphere

was added platinum oxide (Adam's catalyst, 164mg). The reaction mixture was purged with H_2 (via balloon) and stirred for 2 hours. Proton NMR analysis of an aliquot showed incomplete reduction. An additional 82mg of PtO_2 was added and the solution stirred under a H_2 atmosphere for another hour. The reaction mixture was filtered over Celite, rinsed with 10% MeOH in DCM and concentrated. The crude material purified by silica gel chromatography eluting with 1% MeOH in DCM to give 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.61 (m, 4H), 1.78 (m, 4H), 2.38 (m, 1H), 3.92 (m, 4H).

INTERMEDIATE 73

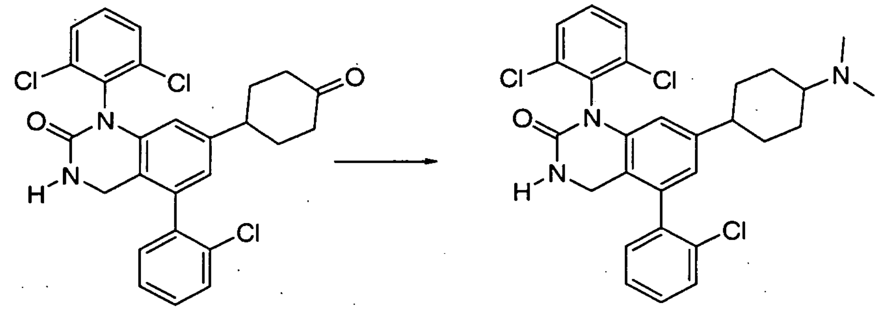
1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone



To a suspension of 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone (248mg, 0.456 mmol) (**INTERMEDIATE 72**) in acetone (12 mL) was added Amberlyst-15 (130mg). The mixture was stirred at RT for 6 hours at which time the reaction mixture became homogeneous. The solution was filtered and the solvent concentrated. The crude material was purified by silica gel chromatography eluting with 1:4 acetone:hexanes followed by 1:3 acetone:hexanes to give 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.78 (m, 2H), 2.14 (m, 2H), 2.4 (m, 4H) 2.86 (m, 1H). MS(ES) 499 (M+H); LC 1: 3.19min.

EXAMPLE 51

1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-dimethylaminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone



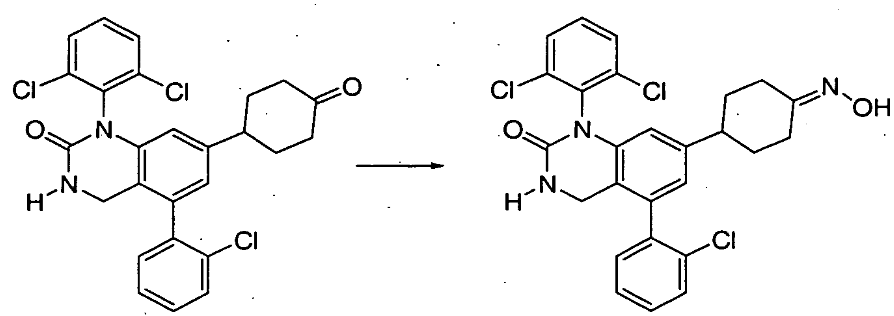
To a solution of 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone (33mg, 0.066 mmol) (**INTERMEDIATE 73**) in 1,2-dichloroethane (1.0mL) at RT (under a nitrogen atmosphere) was added dimethylamine hydrochloride (11mg, 0.132 mmol) followed by triethylamine (18μL, 0.132 mmol). The reaction mixture was stirred for 10min then $NaBH(OAc)_3$ (21mg, 0.099 mmol) was added to the reaction. After 1.5h the reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution followed by brine, and dried over Na_2SO_4. The crude residue was purified by preparative thin layer chromatography using 5% MeOH in DCM as the eluent to give 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-dimethylaminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone (diastereomer A and diastereomer B).

<u>Diastereomer A</u> ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.60 (brm, 4H), 1.72 (brm, 2H), 1.91 (brm, 2H), 2.34 (s, 6H), 2.42 (brm, 1H), 2.66 (brs, 1H). MS(ES) 528 (M+H); LC 1: 2.296 min.

<u>Diastereomer B</u> ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.40 (m, 2H), 1.62 (brm, 2H), 2.02 (m, 2H), 2.29 (m, 2H), 2.41 (m, 1H), 2.71 (s, 6H), 3.01 (m, 1H). MS(ES) 528 (M+H); LC 1: 2.313 min.

INTERMEDIATE 74

<u>1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-hydroxyiminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone</u>



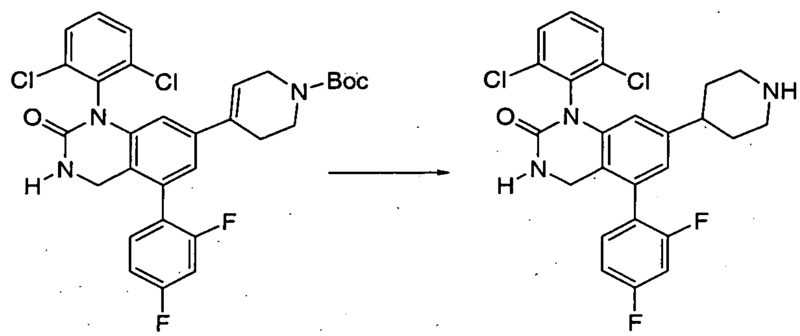
To a solution of hydroxylamine hydrochloride (29mg, 0.416 mmol) in methanol (1.0 mL) was added solid $NaHCO_3$ (37mg, 0.437 mmol). After stirring 15 minutes at RT 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone (52mg, 0.104 mmol) (**INTERMEDIATE 73**) was added. After stirring 18 hours the solution was concentrated. The residue was suspended in DCM and the solid filtered. The filtrate solution was concentrated and the residue purified by preparative thin layer chromatography using 5% MeOH in DCM as the eluent to give 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-hydroxyiminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone.

^{1}H NMR ($CDCl_3$, 500MHz): selected data 1.53 (m, 2H), 1.87 (dt, 1H, J = 5.4, 14.2 Hz), 1.98 (m, 2H), 2.19 (m, 1H), 2.57 (brd, 1H, J = 14.4 Hz), 2.64 (m, 1H), 3.38 (brd, 1H, J = 15.2 Hz).

MS(ES) 514 (M+H); LC 1: 3.027min.

EXAMPLE 52

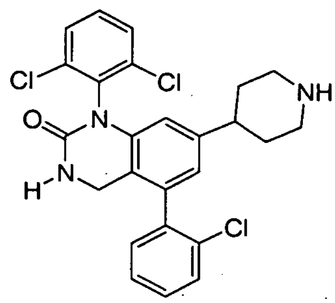
<u>1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-(1-Boc-1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 41** Step A) as described in **INTERMEDIATE 72** (replacing Pt_2O with 10%Pd on carbon and EtOAc with MeOH). The *tert*-butoxycarbonyl substituent was removed as described in **EXAMPLE 34** Step B. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.41-1.52 (m, 2H), 1.64(1H, NH), 1.70-1.79 (m, 2H), 2.48(m, 1H), 2.66(app t, 2H, J=12.1Hz), 3.12 (app d, 2H, J=11.9Hz), 4.21-4.58 (br m, 2H), 5.19 (s, 1H), 6.03 (s, 1H), 6.82 (s, 1H), 6.91-7.01 (m, 2H), 7.28-7.33 (m, 1H), 7.40 (app t, 1H, J=8.0Hz), 7.54 (d, 2H, J=8.3Hz). MS(ES) 488 (M+H); LC 1: 2.14min.

EXAMPLE 53

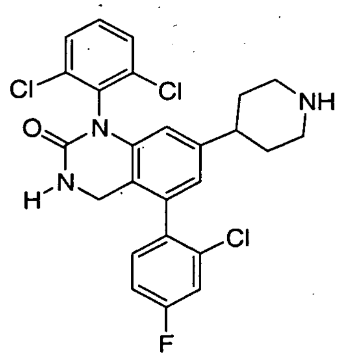
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1-Boc-1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 42** Step A) as described in **INTERMEDIATE 72** (replacing Pt_2O with 10%Pd on carbon and EtOAc with MeOH). The *tert*-butoxycarbonyl substituent was removed as described in **EXAMPLE 34** Step B. ^{1}H NMR(CD_3OD, 500MHz): δ 1.40-1.51 (m, 2H), 1.67-1.73 (m, 2H), 2.48-2.56 (m, 1H), 2.57-2.67 (m, 2H), 3.01-3.07 (m, 2H), 4.20 (d, 1H, J=14.8Hz), 4.27 (d, 1H, J=14.9Hz), 5.99 (d, 1H, J=1.1Hz), 6.78 (d, 1H, J=1.1Hz), 7.30 (m, 1H), 7.38-7.42 (m, 2H), 7.43-7.56 (m, 2H), 7.58-7.63 (m, 2H). MS(ES) 486 (M+H); LC 1: 2.14min.

EXAMPLE 54

1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone

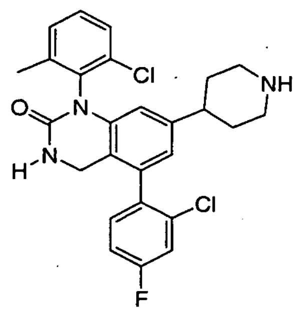


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-Boc-1,2,3,6-tetrahydro-4-pyridinyl)-3,4-dihydro-2(1H)-

quinazolinone (EXAMPLE 43 Step A) as described in **INTERMEDIATE 72** (replacing Pt_2O with 10%Pd on carbon and EtOAc with MeOH). The *tert*-butoxycarbonyl substituent was removed as described in **EXAMPLE 34** Step B. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.6 (m, 4H), 2.51 (m, 1H), 2.73 (m, 2H), 3.24 (m, 2H), 4.22 (d, 1H, J=14.4Hz), 4.39 (d, 1H, J=14.4Hz), 5.13 (s, 1H), 6.00 (d, 1H, J=0.9Hz), 6.74 (d, 1H, J=0.9Hz), 7.03-7.11 (m, 1H), 7.25-7.31 (m, 2H), 7.39 (t, 1H, J=8.1Hz), 7.54 (d, 2H, J=8.2Hz). MS(ES) 504 (M+H); LC 1: 2.04min.

EXAMPLE 55

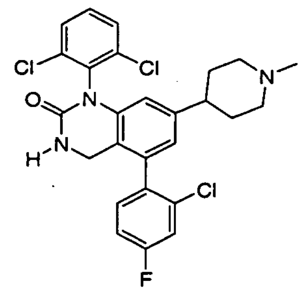
1-(2-chlorophenyl-6-methyl)-5-(2-chloro-4-fluoro-phenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 54** (replacing 2,6-dichlorophenyl isocyanate with 2-chloro-6-methyl isocyanate in **INTERMEDIATE 21**). ^{1}H NMR($CDCl_3$, 500MHz): δ 1.52-1.61 (m, 2H), 1.72-1.81 (m, 2H), 2.27 (d, 3H, J=2.3 Hz), 2.42-2.52 (m, 1H), 2.69 (t, 2H, J=12.3 Hz), 3.22 (d, 2H, J=12.1 Hz), 4.17-4.45 (m, 2H), 5.11-5.13 (m, 1H), 5.98 (s, 1H), 6.71 (s, 1H), 7.08 (td, 1H, J=11.0, 2.8 Hz), 7.25-7.30 (m, 2H), 7.31 (t, 2H, J=7.6 Hz), 7.44 (dd, 1H, J=7.3, 2.0 Hz). MS(ES) 484 (M+H); LC 1: 2.03 min

EXAMPLE 56

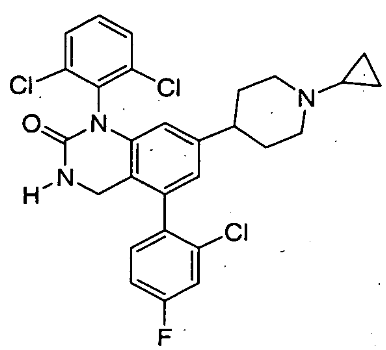
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-methyl-4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 54**) as described in **EXAMPLE 15**. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.61 (m, 2H), 1.73 (m, 2H), 1.96 (m, 2H), 2.27 (s, 3H), 2.35 (m, 1H), 2.89 (m, 2H), 4.22 (app dd, 1H, J=1.8, 14.2 Hz), 4.39 (app dd, 1H, J=1.4, 14.2Hz), 5.19 (s, 1H), 6.03 (d, 1H, J=0.9Hz), 6.74 (d, 1H, J=0.9Hz), 7.05-7.10 (m, 1H), 7.24-7.31 (m, 2H), 7.39(t, 1H, J=8.1Hz), 7.53 (d, 2H, 8.2Hz). MS(ES) 518 (M+H); LC 1: 2.04 min.

EXAMPLE 57

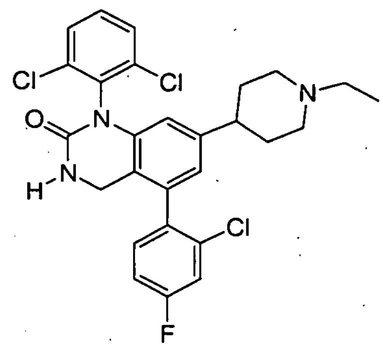
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-cyclopropyl-4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 54**) as described by M. L. Gillaspy, B. A. Lefker, et al *Tetrahedron Letters* **1995**, V36 (41), 7399-7402. ^{1}H NMR($CDCl_3$, 500MHz): δ 0.39-0.48 (brm, 4H), 1.52-1.68 (brm, 3H), 1.75(d, 2H, J=10.9 Hz), 2.22 (brs, 2H), 2.41 (t, 1H, J=1.8 Hz), 3.11 (brs, 2H), 4.24 (app dd, 1H, J=1.7,14.3Hz), 4.38 (app dd, 1H, J=1.5,14.3Hz), 5.10 (s, 1H), 6.02 (d, 1H, J=1.2Hz), 6.75 (s, 1H), 7.05-7.10 (m, 1H), 7.24-7.30 (m, 2H), 7.39 (t, 1H, J=8.1Hz), 7.53 (d, 2H, J=8.0Hz). MS(ES) 544 (M+H); LC 1: 2.25min.

EXAMPLE 58

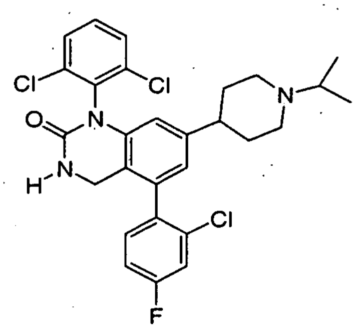
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(N-ethyl)piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



To 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone (15.3mg, 0.030mmol) (**EXAMPLE 54**) in 1mL ethanol was added bromoethane (20.1mg, 0.184mmol) and potassium carbonate (30mg, 0.217mmol). After stirring at room temperature for 12 hours the reaction mixture was partition between water and ethyl acetate. The phases were separated and the organic phase washed with brine and concentrated. The residue was purified by preparative thin layer chromatography using $CHCl_3$/MeOH/NH_4OH (87/12/1) as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(N-ethyl)piperidinyl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 1.08 (t, 3H, J=7.2 Hz); 1.63 (appt, 2H, J=11.7 Hz); 1.70-1.78 (m, 2H); 1.91-1.93 (m, 2H); 2.38-2.41 (m, 3H); 3.00-3.02 (d, 2H, J=10.7 Hz). MS(ES) 532 (M+H); LC 1: 2.23 min.

EXAMPLE 59

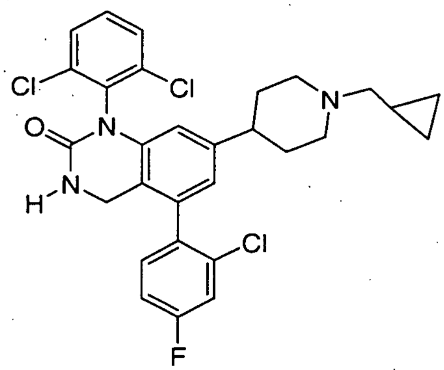
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(1-isopropyl)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 58** (replacing bromoethane with 2-iodopropane). ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 1.04 (d, 6H, J=6.4 Hz); 1.59 (app t, 2H, J=11.8 Hz); 1.73-1.78 (m, 2H); 2.13-2.18 (m, 2H), 2.29-2.39 (m, 1H); 2.62-2.71 (m, 1H); 2.93-2.95 (m, 2H). MS(ES) 546 (M+H); LC 1: 2.32min.

EXAMPLE 59B

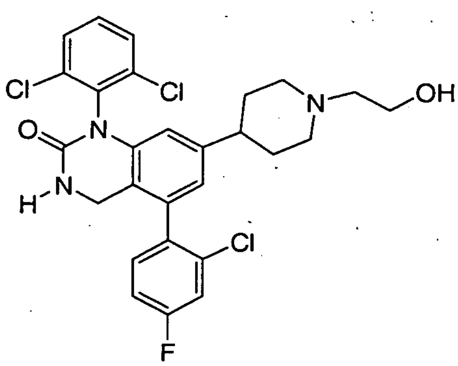
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(1-cyclopropylmethyl)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 58** (replacing bromoethane with cyclopropylmethyl bromide). ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 0.40 (brs, 2H); 0.76 (brs, 2H); 1.24 (brs, 1H); 1.85-2.02 (brm, 2H), 2.20-2.95 (brm, 7H); 3.58-3.81 (brm, 2H). MS(ES) 558 (M+H); LC 1: 2.48min.

EXAMPLE 60

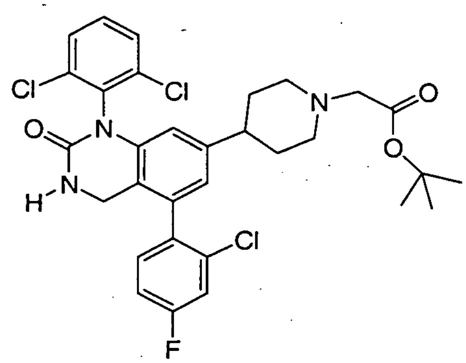
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(N-2-hydroxyethyl)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 58** (replacing bromoethane with 2-bromoethanol). ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 1.53-1.66 (m, 2H); 1.71-1.80 (m, 2H); 2.07-2.12 (m, 2H); 2.31-2.42 (m, 1H); 2.50-2.54 (m, 2H); 2.95-2.97 (m, 2H); 3.60-3.62 (m, 2H). MS(ES) 548 (M+H); LC 1: 2.13min.

EXAMPLE 61

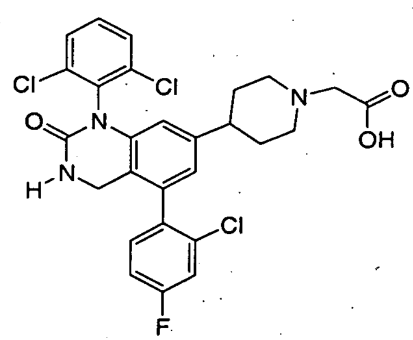
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(N-t-butylacetate)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared as described in **EXAMPLE 58** (replacing bromoethane with t-butyl bromoacetate). ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 1.47 (s, 9H); 1.62-1.69 (m, 4H); 2.19 (app t, 2H, J=1.8 Hz); 2.31-2.40 (m, 1H); 3.05 (d, 2H, J=11.0 Hz); 3.11 (s, 2H). MS(ES) 618 (M+H); LC 1: 2.65min

EXAMPLE 62

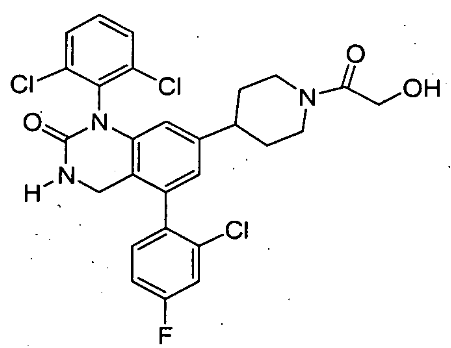
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(1-acetic acid)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluoro-phenyl)-7-(N-(t-butylacetate)-1,2,3,6-tetrahydro-5-pyridinyl)-3,4-dihydro-2(1H)-quinazolinone (11.7mg, 0.0189mmol) (**EXAMPLE 61**) in 1mL 1/1 TFA/DCM was stirred at room temperature for 12 h. The solution was concentrated and the residue washed with ethyl ether to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-(1-acetic acid)-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): selected data δ 1.81-1.92 (m, 2H); 2.00 (app d, 2H, J=12.3 Hz); 2.77 (t, 1H, J=1.8 Hz); 3.30 (t, 2H, J=1.8 Hz); 3.64 (d, 2H, J=10.3 Hz); 4.23 (ABq, 2H, J=15.0 Hz). MS(ES) 562 (M+H); LC 1: 2.11min.

EXAMPLE 63

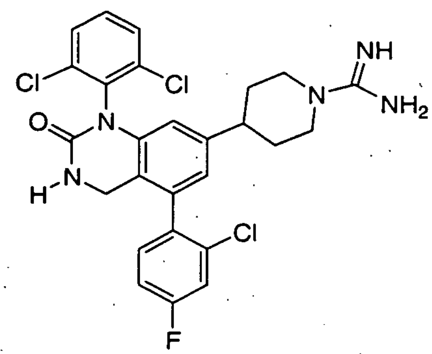
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-hydroxyacetyl-4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 54**) as described in **EXAMPLE 14**. ^1H NMR($CDCl_3$, 500MHz): selected data δ 1.42-1.57 (m, 2H); 1.84-1.87 (m, 2H); 2.63 (t, 1H, 13.3 Hz); 3.03 (t, 1H, J=13.8 Hz); 3.55 (d, 1H, J=13.8 Hz); 4.15 (ABq, 2H, J=5.3 Hz); 4.68 (d, 1H, J=13.3 Hz). MS(ES) 562 (M+H); LC 1: 2.76min.

EXAMPLE 64

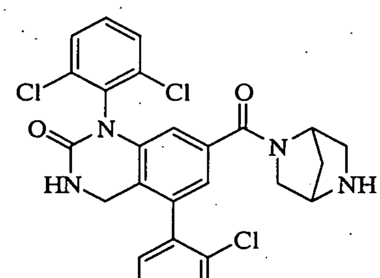
1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-imidine-4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone



To 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone (11.2mg, 0.022mmol) (**EXAMPLE 54**) in 0.5 mL THF was added N,N'-bis-Boc-1-guanylpyrazole (12.6mg, 0.041mmol). The reaction mixture was stirred at 55°C (oil bath) for 12 hours. The solution was concentrated and the residue purified by preparative thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (87/12/1) as the eluent. The isolated material (N-Boc) was stirred in 1mL 1/1 TFA/DCM for 1.5h at RT. The solution was concentrated and the residue purified by preparative thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (87/12/1) as the eluent to give 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-(1-imidine-4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone. ^1H NMR($CDCl_3$, 500MHz): selected data δ 1.55 (m, 2H); 1.84 (d, 2H, 10.7 Hz); 2.75 (m, 1H); 3.12 (t, 2H, J=11.5 Hz); 3.90 (d, 2H, J=13.8 Hz); 4.24 (ABq, 2H, J=8.0 Hz). MS(ES) 546 (M+H); LC 1: 2.20min.

EXAMPLE 65

1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(N-bicyclo[2.2.1]piperazinylcarbonyl)-3,4-dihydro-2(1H)-quinazolinone

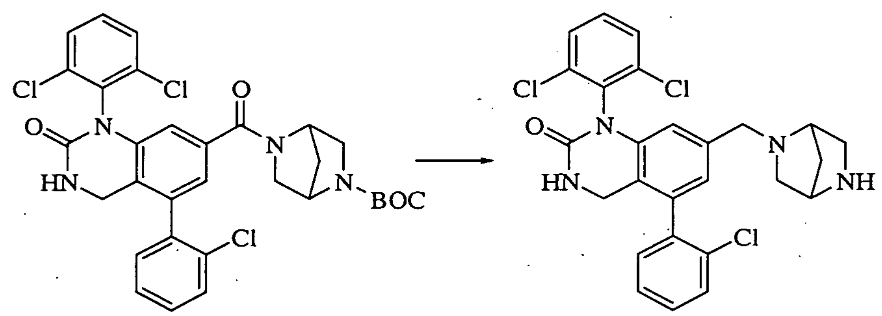


The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-carboxyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 59**)

as described in **EXAMPLE 19** [replacing N-(2-chlorophenyl)piperazine with N-BOC-bicyclo[2.2.1]piperazine]. The *tert*-butoxy carbonyl substituent was subsequently removed as described in **EXAMPLE 34** Step B. ^{1}H NMR($CDCl_3$, 500MHz): selected data δ 2.66-3.24 (m, 3H), 3.27-3.33 (m, 2H), 3.41-3.49 (m,1H), 3.62-3.68 (m, 1H), 3.8-3.9 (m, 1H). MS(ES) 527 (M+H); LC 1: 1.9min.

EXAMPLE 66

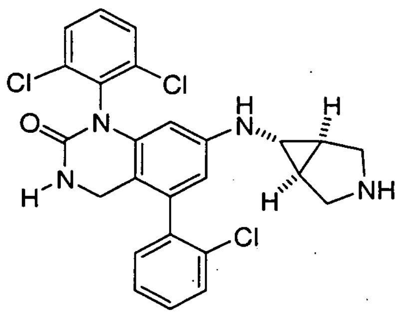
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-bicyclo[2.2.1]piperazinylmethyl -3,4-dihydro-2(1H)-quinazolinone



A solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-[N-BOC-bicyclo[2.2.1]piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinazolinone (52mg, 0.083 mmol) (**EXAMPLE 65**, Step A) and borane-THF complex (2mL of 1.0M solution, 2mmol) was stirred at room temperature for two hours. Methanol (1mL) was added and the mixture was stirred for 10 minutes. The solution was concentrated a solution of TFA (1mL) and methylene chloride (0.5mL) was added. The mixture was stirred at room temperature for 16 hours. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 10 % 2N ammonia in methanol / methylene chloride provided 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-bicyclo[2.2.1]piperazinylmethyl -3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.72 (brd, 1H), 1.85 (d, 1H, J=10.0Hz), 2.64 (d, 1H, J=10.7Hz), 2.80-2.86 (m, 1H), 2.90-2.98 (m, 1H), 3.20 (t, 1H, J=11.2Hz), 3.40 (s, 1H), 3.50 (s, 2H), 3.61 (s, 1H), 3.84 (d, 1H, J=5.3Hz), 4.22-4.30 (m, 1H), 4.38-4.46 (m, 1H), 5.32 (s,1H), 6.14 (s, 1H), 6.88 (s, 1H), 7.28-7.40 (m, 4H), 7.42-7.56 (m, 4H). MS(ES) 513 (M+H); LC 1: 1.78min.

EXAMPLE 67

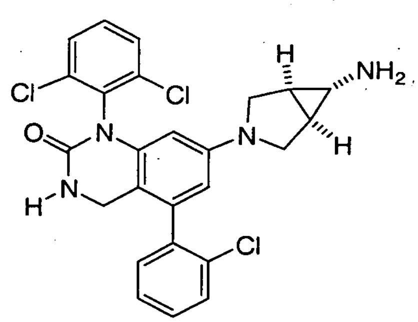
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-amino(azabicyclo[3.1.0]hexane)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) as described in **EXAMPLE 34** (replacing 1-Boc-piperazine with (1α, 5α, 6α)-3-benzyloxycarbonyl-6-amino-3-azabicyclo[3.1.0]hexane). See K. E. Brighty and M. J. Castaldi *Synlett* **1996**, 1097-1099. The benzyloxycarbonyl group was subsequently cleaved with HBr in AcOH. ^{1}H NMR(CD_3OD, 500MHz): selected data δ 1.63 (brm, 2H), 2.03 (s, 1H), 2.93-2.98 (m, 2H), 3.02-3.08 (m, 2H). MS(ES) 499 (M+H); LC 1: 2.07min.

EXAMPLE 68

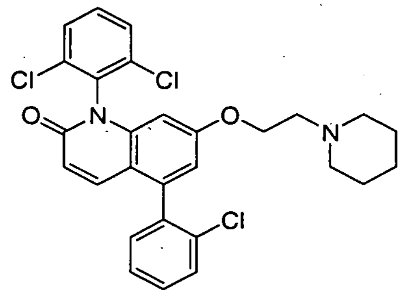
1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(azabicyclo[3.1.0]hexane)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-trifluoromethylsulfonato-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 61**) as described in **EXAMPLE 34** (replacing 1-Boc-piperazine with (1α, 5α, 6α)-6-*tert*-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane). See K. E. Brighty and M. J. Castaldi *Synlett* **1996**, 1097-1099. ^{1}H NMR(CD_3OD, 500MHz): selected data δ 1.60 (s, 2H), 2.06 (s, 1H), 2.99-3.03 (m, 2H), 3.21 (app d, 2H, J=9.2Hz). MS(ES) 499 (M+H); LC 1: 2.27min.

EXAMPLE 69

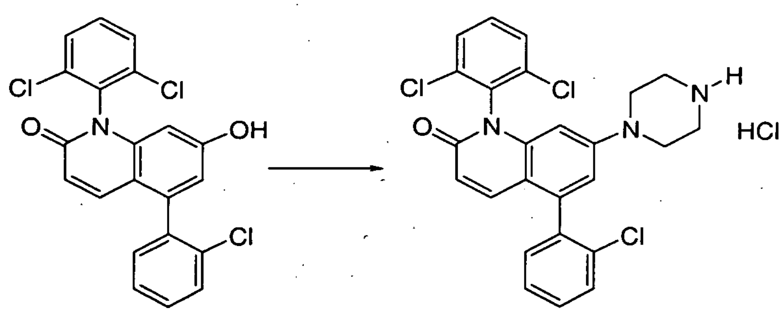
1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-[2-(1-piperidinyl)ethoxy]-2(1*H*)-quinolinone



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 9**), Ph_3P, 1-piperidine ethanol, and diethyl azodicarboxylate by a procedure analogous to that described in **EXAMPLE 2**. Mass spectrum (ESI) 527.1 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.61 (m, 3H); 7.36-7.47 (m, 5H); 6.75 (d, J=2.5 Hz, 1H); 6.53 (d, J=9.5 Hz, 1H); 6.02 (d, J=2.0 Hz, 1H); 4.00 (t, J= 6.0 Hz 2H); 2.69 (t, J= 6.0 Hz 2H); 2.42 (br s, 4H); 1.45-1.65 (m, 6H).

EXAMPLE 70

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperazin(1-yl)-2(1*H*)-quinolinone



Step A: Triflate

To a suspension solution of 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-2(1*H*)-quinolinone (**INTERMEDIATE 9**) (100mg) in DCM (5mL) was added N,N-diisopropylethylamine (0.083mL) and trifluoromethanesulfonic anhydride (0.06mL) at –78°C. After stirring at -78°C for 10min., the mixture was warmed to room temperature and stirred an additional 10min. The reaction was quenched with methanol and concentrated. The residue was purified

by silica gel chromatography (hexanes/ethyl acetate=4/1) to give 82mg of the desired triflate. [1]H NMR($CDCl_3$, 500MHz): δ 7.64 (m, 2 H), 7.59 (d, 1 H), 7.49 (m, 5 H), 7.11 (d, 1 H), 6.77 (d, 1 H), 6.44 (d, 1 H).

Step B: BOC intermediate

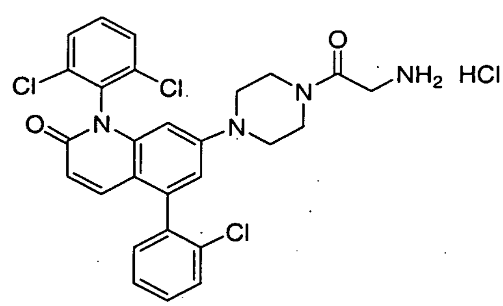
A solution of the triflate from Step A above (80mg) in toluene (3mL) was added tris(dibenzylideneacetone)dipalladium (7mg), 1,1-bis(diphenylphosphino)ferrocene (7mg), sodium t-butoxide (19mg) and 1-t-butoxycarbonylpiperaine (50mg) and heated 100°C for 16h. The resulting reaction mixture was cooled to room temperature and diluted with ethyl acetate. The solution was filtered through celite and concentrated. The residue was purified by silica gel chromatography (hexanes/ethyl acetate=2/1) to give the BOC intermediate coupling product (62mg). [1]H NMR($CDCl_3$, 500MHz): δ 7.56 (m, 3 H), 7.40 (m, 5 H), 6.73 (d, 1 H), 6.50 (d, 1 H), 5.84 (d, 1 H), 3.52 (t, 4 H), 3.13 (t, 4 H), 1.47 (s, 9 H).

Step C: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperazin(1-yl)-2(1*H*)-quinolinone

A solution of the BOC intermediate from Step B above (61mg) in ethyl acetate (3mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture for 30 seconds. The mixture was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was concentrated to remove the ethyl acetate. The residue was the diluted with hexanes and followed by evaporation in vacuo to yield 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperazin(1-yl)-2(1*H*)-quinolinone as a solid.

EXAMPLE 71

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-amino-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone

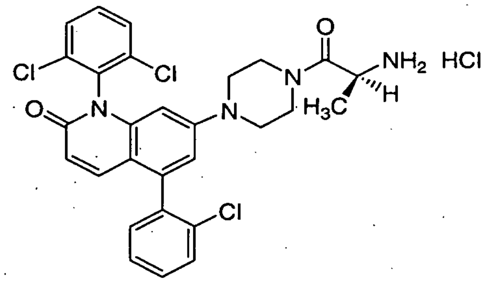


To a solution of **EXAMPLE 70** (5mg), BOP reagent (9mg), Boc-Glycine (3.5mg) in DCM (0.5mL) was added triethylamine (0.003ml). The reaction

was stirred at room temperature for 24h. Removal of the solvent and subsequent purification by preparative thin layer chromatography (hexanes/ethyl acetate=1/1) provided the desired Boc Intermediate coupling product. A solution of the Boc intermediate in ethyl acetate (1mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture for 30 seconds. The mixture was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was concentrated to remove the ethyl acetate. The residue was the diluted with hexanes and followed by evaporation in vacuo to give 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-amino-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone. ^{1}H NMR(CD_3OD, 500MHz): δ 7.71 (m, 2 H), 7.60 (m, 2 H), 7.45 (m, 4 H), 6.91 (d, 1 H), 6.45 (d, 1 H), 5.90 (d, 1 H), 3.94 (s, 2 H), 3.70 (t, 2 H), 3.54 (t, 2 H), 3.25 (t, 2 H), 3.21 (t, 2 H). MS(ES) 542 (M+H).

EXAMPLE 72

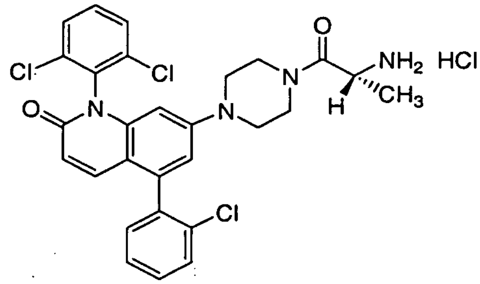
<u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-amino-2-methyl-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone</u>



The title compound was prepared as described in **EXAMPLE 71** (replacing Boc-Glycine with Boc-L-Alanine). ^{1}H NMR(CD_3OD, 500MHz): δ 7.72 (m, 2 H), 7.60 (m, 2 H), 7.44 (m, 4 H), 6.92 (d, 1 H), 6.45 (d, 1 H), 5.91 (d, 1 H), 4.39 (q, 1 H), 3.61 (m, 4 H), 3.25 (m, 4 H), 1.44 (d, 3 H). MS(ES) 556 (M+H).

EXAMPLE 73

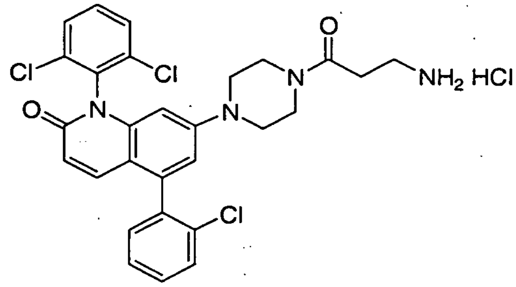
<u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-amino-2-methyl-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone</u>



The title compound was prepared as described in **EXAMPLE 71** (replacing Boc-Glycine with Boc-D-Alanine). ^{1}H NMR(CD_3OD, 500MHz): δ 7.72 (m, 2 H), 7.60 (m, 2 H), 7.44 (m, 4 H), 6.92 (d, 1 H), 6.45 (d, 1 H), 5.91 (d, 1 H), 4.39 (q, 1 H), 3.61 (m, 4 H), 3.25 (m, 4 H), 1.44 (d, 3 H). MS(ES) 556 (M+H).

EXAMPLE 74

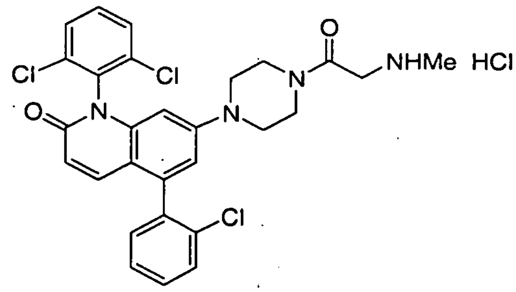
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(3-amino-propan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone



The title compound was prepared as described in **EXAMPLE 71** (replacing Boc-Glycine with Boc-β-Alanine). ^{1}H NMR(CD_3OD, 500MHz): δ 7.71 (m, 2 H), 7.60 (m, 2 H), 7.45 (m, 4 H), 6.91 (d, 1 H), 6.44 (d, 1 H), 5.90 (d, 1 H), 3.68 (brs, 2 H), 3.61 (brs, 2 H), 3.25 (brs, 2 H), 3.18 (brs, 2 H), 2.79 (t, 2 H), 2.71 (t, 2 H). MS(ES) 556 (M+H).

EXAMPLE 75

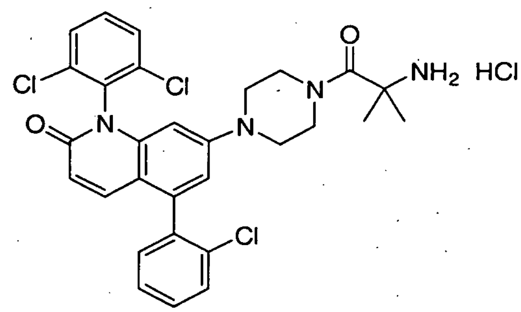
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-methylamino-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone



The title compound was prepared as described in **EXAMPLE 71** (replacing Boc-Glycine with Boc-Sarcosine). ^{1}H NMR(CD_3OD, 500MHz): δ 7.71 (m, 2 H), 7.60 (m, 2 H), 7.45 (m, 4 H), 6.91 (d, 1 H), 6.44 (d, 1 H), 5.91 (d, 1 H), 4.07 (s, 2 H), 3.69 (t, 2 H), 3.55 (t, 2 H), 3.25 (t, 2 H), 3.22 (t, 2 H), 2.73 (s, 3 H). MS(ES) 556 (M+H).

EXAMPLE 76

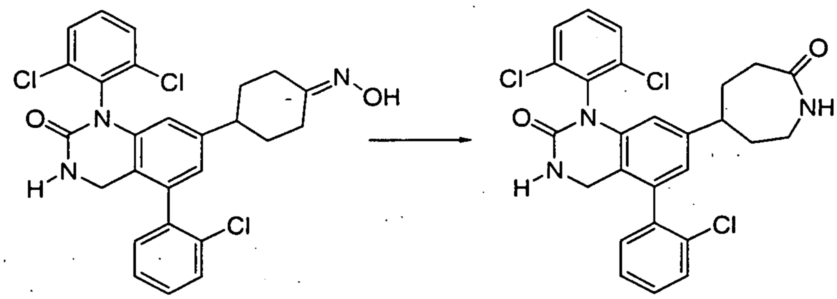
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-(2-amino-2,2-dimethyl-ethan-1-one)-piperazin(4-yl))-2(1*H*)-quinolinone



The title compound was prepared as described in **EXAMPLE 71** (replacing Boc-Glycine with Boc-α–methylalanine). ^{1}H NMR(CD_3OD, 500MHz): δ 7.71 (m, 2 H), 7.60 (m, 2 H), 7.48 (m, 4 H), 6.91 (d, 1 H), 6.45 (d, 1 H), 5.92 (d, 1 H), 3.75 (brs, 4 H), 3.22 (brs, 4 H), 1.65 (s, 3 H), 1.57 (s, 3 H). MS(ES) 570 (M+H).

EXAMPLE 77

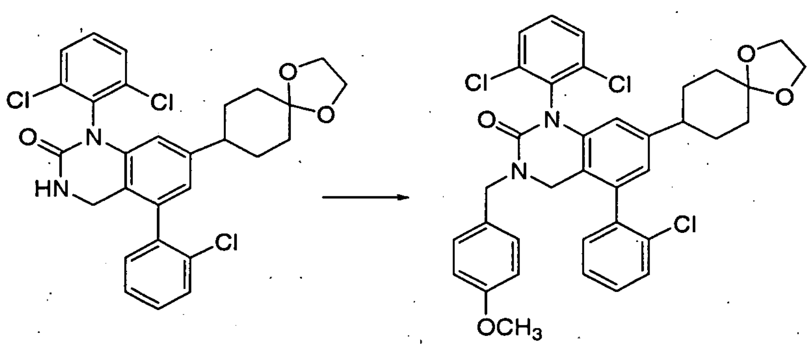
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-(2-oxoazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone



To a solution of 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-hydroxyiminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone (46mg, 0.089 mmol) in DCM (2.0mL) at 0°C was added methanesulfonyl chloride (35 μL, 0.445 mmol) followed by pyridine (36μL, 0.445 mmol). The ice bath was removed after 10 minutes and the reaction mixture was stirred at RT for 20hours. A few drops of water was added to the reaction mixture and the solution stirred for an additional 30 minutes. The solution was concentrated and the residue suspended in DCM. The solid was filtered and rinsed with EtOAc. The filtrate solution was concentrated and the crude residue purified by preparative thin layer chromatography 3% MeOH in DCM to give 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-(2-oxoazepane-3-yl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.55 (m, 2H), 1.92 (m, 2H), 2.49 (m, 2H), 2.59 (m, 1H), 3.25 (m, 2H). MS(ES) 514 (M+H); LC 1: 2.592min.

INTERMEDIATE 75

<u>1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone</u>



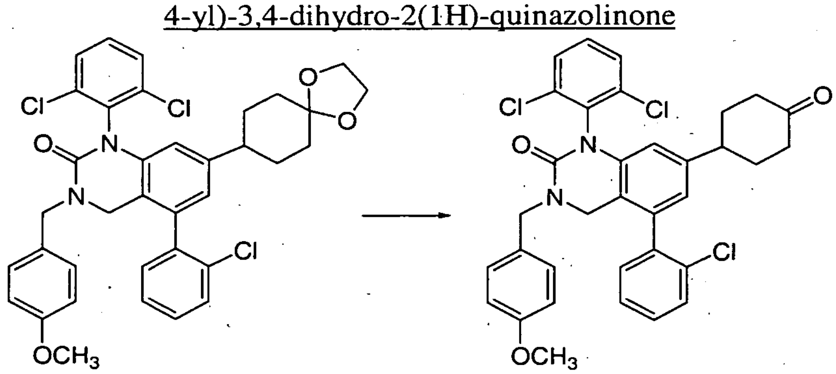
To a solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 72**) (102mg, 0.187mmol) in DMF (2mL) at 0°C was added NaH (15mg, 0.375mmol).

The resulting reaction mixture was stirred until it became homogeneous. 4-Methoxybenzyl chloride (51µL, 0.375mmol) was then added and the ice bath was removed. The reaction was stirred for 2 hours at RT, cooled down with an ice bath, and quenched with H_2O. It was diluted with CH_2Cl_2, separated layers, and the organic layer was washed with H_2O three times. The combined aqueous layer was back-extracted once with CH_2Cl_2, and the combined organic layer was washed with brine and dried over Na_2SO_4. The crude material was purified by preparative TLC eluting with 1:2 acetone:hexanes to obtain 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone.

MS(ES) 665 (M+H); LC 1: 4.56min.

INTERMEDIATE 76

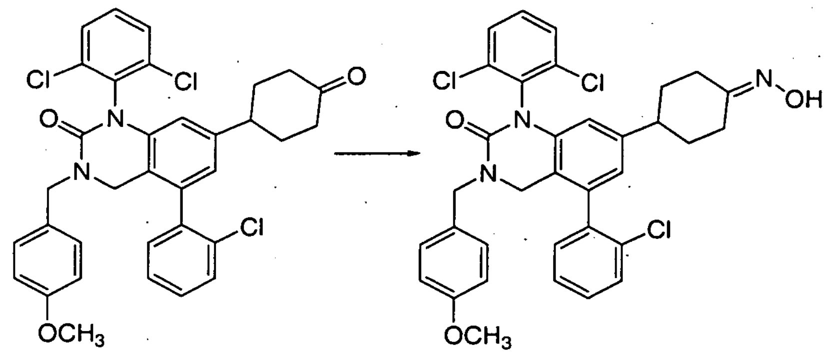
1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1,4-dioxaspiro(4.5)dec-8-yl)-3,4-dihydro-2(1H)-quinazolinone **(INTERMEDIATE 75)** according to the procedure described in **INTERMEDIATE 73.** ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.77 (m, 2H), 2.13 (m, 2H), 2.4 (m, 4H), 2.86 (m, 1H), 3.78 (s, 3H), 4.4 (d, J = 4.8 Hz, 1H), 4.65 (d, J = 4.8 Hz, 1H). MS(ES) 619 (M+H); LC 1: 3.92min.

INTERMEDIATE 77

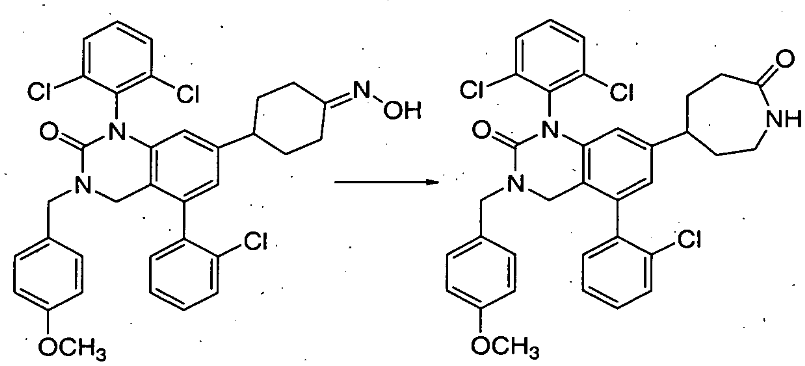
1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-hydroxyiminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-cyclohexanon-4-yl)-3,4-dihydro-2(1H)-quinazolinone **(INTERMEDIATE 76)** according to the procedure described in **INTERMEDIATE 74**. [1]H NMR ($CDCl_3$, 500MHz): selected data δ 1.49 (m, 2H), 1.80 (dt, 1H, J = 5.0, 14.2 Hz, 1H), 1.97 (m, 2H), 2.16 (m, 1H), 2.45 (brd, J = 12.5 Hz, 1H), 2.62 (m, 1H), 3.37 (brd, 1H, J = 14.2 Hz), 3.78 (s, 3H). MS(ES) 634 (M+H); LC 1: 3.76min.

INTERMEDIATE 78

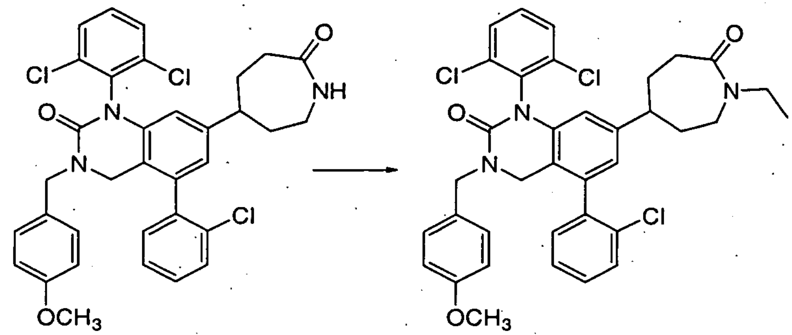
<u>1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(2-oxoazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone</u>



The title compound was prepared from 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-hydroxyiminocyclohexan-4-yl)-3,4-dihydro-2(1H)-quinazolinone **(INTERMEDIATE 77)** according to the procedure described in the **EXAMPLE 77**. [1]H NMR ($CDCl_3$, 500MHz): selected data δ 1.55 (m, 2H), 1.92 (m, 2H), 2.49 (m, 2H), 2.59 (m, 1H), 3.25 (m, 2H), 3.78 (s, 3H). MS(ES) 634 (M+H); LC 1: 3.48 min.

INTERMEDIATE 79

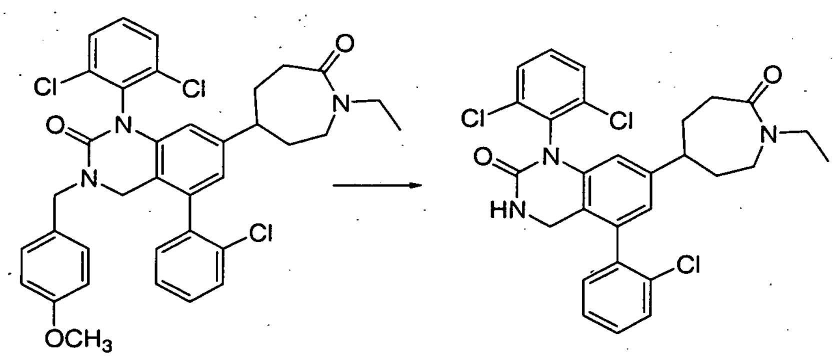
1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-ethyl-2-oxoazepane-5-yl)-3,4-dihydro-2(1H)-quinazolinone



The title compound was prepared from 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(2-oxoazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone **(INTERMEDIATE 78)** according to the procedure described in **INTERMEDIATE 75** using ethyl bromide. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.08 (dt, J = 1.3, 7.1 Hz, 3H), 1.52 (m, 2H), 1.93 (m, 2H), 2.56 (m, 3H), 3.23 (dd, J = 5.7, 15.1 Hz, 1H), 3.33 (m, 1H), 3.48 (m, 2H), 3.78 (s, 3H). MS(ES) 664 (M+H); LC 1: 3.71min.

EXAMPLE 78

1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-ethyl-2-oxoazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone

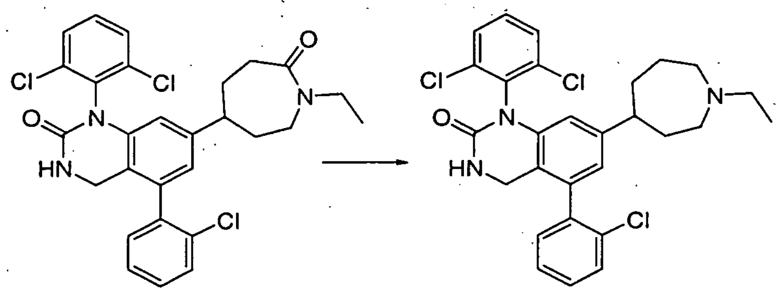


The title compound was prepared from 1-(2,6-Dichlorophenyl)-3-(4-methoxybenzyl)-5-(2-chlorophenyl)-7-(1-ethyl-2-oxoazepane-5-yl)-3,4-dihydro-2(1H)-quinazolinone **(INTERMEDIATE 79)** according to the procedure described in **INTERMEDIATE 23**. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.08 (dt, J = 1.8, 7.1 Hz, 3H), 1.52 (m, 2H), 1.94 (m, 2H), 2.55 (m, 3H), 3.23 (dd, J = 5.9, 15.3 Hz,

1H), 3.34 (m, 1H), 3.49 (m, 2H), 4.22 (apparent m, 1H), 4.37 (apparent m, 1H). MS(ES) 544 (M+H); LC 1: 3.06 min.

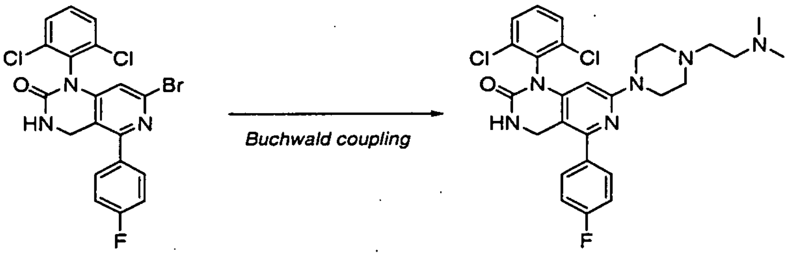
EXAMPLE 79

1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-ethylazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone



To a solution of 1-(2,6-dichlorophenyl)-5-(2-chlorophenyl)-7-(1-ethyl-2-oxoazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone (**EXAMPLE 78**) (9.7mg, 0.018mmol) in THF (0.2mL) under N_2 atmosphere was added BH_3•THF (88μL, 1.0M solution in THF). The reaction was stirred at RT overnight. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2. The resulting solution was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was re-dissolved in CH_2Cl_2 (0.5mL) then cooled down to 0°C. To this was added Et_3SiH (3μL, 0.036mmol) followed by BF_3•Et_2O (2.5μL, 0.04mmol), and the mixture was slowly warmed to RT over 2 hours. It was quenched with saturated solution of $NaHCO_3$, then extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and dried over Na_2SO_4. The crude residue was purified by preparative TLC eluting with 5% 2M NH_3 in MeOH/CH_2Cl_2 to obtain 1-(2,6-Dichlorophenyl)-5-(2-chlorophenyl)-7-(1-ethylazepan-5-yl)-3,4-dihydro-2(1H)-quinazolinone. ^{1}H NMR ($CDCl_3$, 500MHz): selected data δ 1.03 (t, J = 7.1 Hz, 3H), 1.6 – 1.87 (m, 6H), 2.52 (q, J = 7.1 Hz, 2H), 2.56 – 2.73 (m, 5H). MS(ES) 530 (M+H); LC 1: 2.36min.

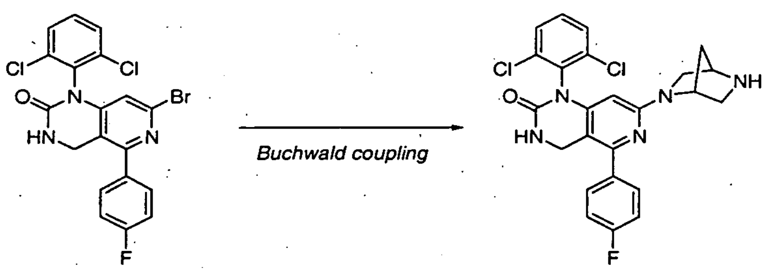
EXAMPLE 80



EXAMPLE 80

Referring to scheme 13, to $Pd_2(DBA)_3$ (0.1mmole) and BINAP (0.2mmole) was added 0.5mL of deoxygenated toluene. The resulting reaction mixture was evacuated and back filled with argon. The reaction mixture was heated under an argon atmosphere, at 40°C. After 20min heating, a clear homogenous solution resulted. The reaction mixture was brought to room temperature and charged with sodium t-butoxide (1.0mmole) and 4-dimethyl amino ethyl-piperazine (1.2mmole) followed by addition of the aryl bromide (1.0mmole) as a solution in 3.0 mL of toluene. The reaction mixture was evacuated and back filled with argon a few times. The reaction mixture was heated under argon at 80°C for 12h. TLC analysis was used to measure the consumption of starting material. The reaction mixture was diluted with 8.0mL of ethyl acetate and extracted with brine (5.0mL x 3). The organic phase was dried over sodium sulphate and concentrated. The residue was purified by flash column chromatography (gradient: 0 – 7% methanol in dichloromethane) to yield **EXAMPLE 80**. ^{1}H NMR ($CDCl_3$, 500MHz, ppm): 7.55 – 7.49 (4H, m); 7.40 (1H, t, 8 Hz); 7.15 (2H, m); 5.31 (1H, s); 5.29 (1H, bs); 4.55 (2H, bs); 3.41 (4H, bs); 2.56 – 2.51 (8H, m); 2.36 (6H, bs). MS : [M+H] = 543.0

EXAMPLE 81



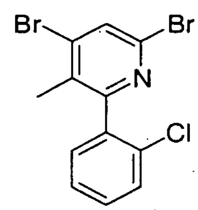
EXAMPLE 81

EXAMPLE 81 was made by following the procedure described above for **EXAMPLE 80** using the corresponding N-boc-bridged piperazine. The Buchwald product obtained in the previous step was dissolved in 15mL of TFA and stirred at

room temperature. The consumption of starting material was monitored by TLC. After completion of reaction as indicated by TLC, the reaction mixture was evaporated and the resulting residue was purified by RP-HPLC. The **EXAMPLE 81** was obtained either by lyophilization or evaporation of the eluants. The free base was obtained by neitralization, extraction into organic phase and evaporation. ^{1}H NMR ($CDCl_3$, 500MHz, ppm): 7.55 – 7.49 (4H, m); 7.40 (1H, t, 8 Hz); 7.15 (2H, m); 5.92 (1H, bs); 4.98 (1H, s); 4.81 (1H, bs); 4.51 (2H, bs); 3.62 (3H, m); 3.22 (3H, bs); 1.95 (2H, bs). MS : [M+H] = 485.0

COMPOUND VV-1

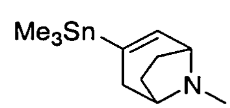
4,6-dibromo-3-(bromomethyl)-2-(2-chloro-phenyl)pyridine



This compound was prepared in a similar fashion as **COMPOUND PS** below. Data: 1H NMR: 7.8 (1H, s); 7.2 – 7.5 (4H, m); 2.2 (3H, s); LCMS: [M+H] = 360.

COMPOUND VV-2

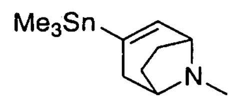
3-trimethylstannyl-8-methyl-8-azabicyclo[3.2.1]oct-2-ene



This compound was prepared in a similar fashion as **INTERMEDIATE 69** starting from commercially available tropinone. Data: 1H NMR: 5.95 (1H, bs); 4.15 (1H, m); 4.09 (1H, m); 2.85 (3H, s); 2.65 – 1.8 (6H, m); 0.22 (9H, t, J = 24 Hz); LCMS [M+H] = 288.

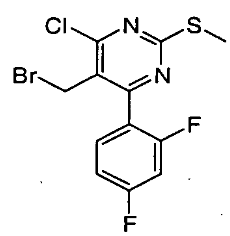
COMPOUND VV-2

3-trimethylstannyl-8-methyl-8-azabicyclo[3.2.1]oct-2-ene



This compound was prepared in a similar fashion as **INTERMEDIATE 69** starting from commercially available tropinone. Data: 1H NMR: 5.95 (1H, bs); 4.15 (1H, m); 4.09 (1H, m); 2.85 (3H, s); 2.65 – 1.8 (6H, m); 0.22 (9H, t, J = 24 Hz); LCMS [M+H] = 288.

COMPOUND VV-3



Step A: Ethyl-3-(2,4-difluorophenyl)-2-methyl-3-oxopropanoate

2,4-difluorobenzoic acid (25g, 158.1mmole) was dissolved 100mL of THF followed by careful addition of carbonyl diimidazolide (27g, 166mmole). This reaction was allowed to stir for 6h. In another flask 32g of ethyl hydrogen malonate was dissolved in 100mL THF followed by careful addition of magnesium ethoxide (9.44g, 82.5mmole). This reaction was allowed to stir for 2h then evaporated to yield a fluffy white powder. This powder was added to the first reaction flask containing the acid imidazolide. The reaction was allowed to stir overnight (10h). The reaction was quenched with 1N HCl and the resulting was extracted with ethyl acetate, combined organic extracts were dried and stripped to yield a colorless oil. LCMS [M+H] = 229.

19g of the compound obtained above was dissolved in 100mL THF followed by careful addition of NaH (4g, 100mmole) at $0^{o}C$. After all the addition of NaH, methyl iodide(6.2mL, 100mmole) was added. The reaction was stirred at rt for 12h. An additional amount of NaH (4g, 100mmole) was added followed by addition of MeI (6.2mL, 100mmole). The reaction was stirred another 12h. The reaction was carefully quenched and subjected to standard work up. The resulting oil was taken into the next step without further purification. LCMS : [M+H] = 243.

Step B: 6-(2,4-difluorophenyl)-5-methyl2-(methylthio)pyrimidin-4-ol

Ethyl-3-(2,4-difluorophenyl)-2-methyl-3-oxopropanoate obtained above was refluxed with thiourea (6.85g, 90mmole) and sodium ethoxide (12.25g, 180mmole) in 75mL of ethanol for 2h. The reaction mixture was cooled to room temperature and concentrated. The residue was dissolved in water, acidified and extrated into ethyl acetate which was concentrated and this polar solid obtained was suspended in water (50mL) followed by addition of KOH (5.0g, 90mmole) and then MeI (5.6mL, 90mmole). The reaction was stirred for 2h at rt. As the reaction proceeded the reaction mixture became turbid. After 2h the reaction was cooled to 0°C, acidified, and extracted into ethyl acetate. The combined extracts were concentrated and subjected to filtration on a pad of silica gel eluting with ethyl acetate. The combined eluants were concentrated to provide a white solid. Data LCMS = [M+H] = 255.

Step C: 4-Chloro-6-(2,4-difluorophenyl)-5-methyl-2-(methylthio)pyrimidine

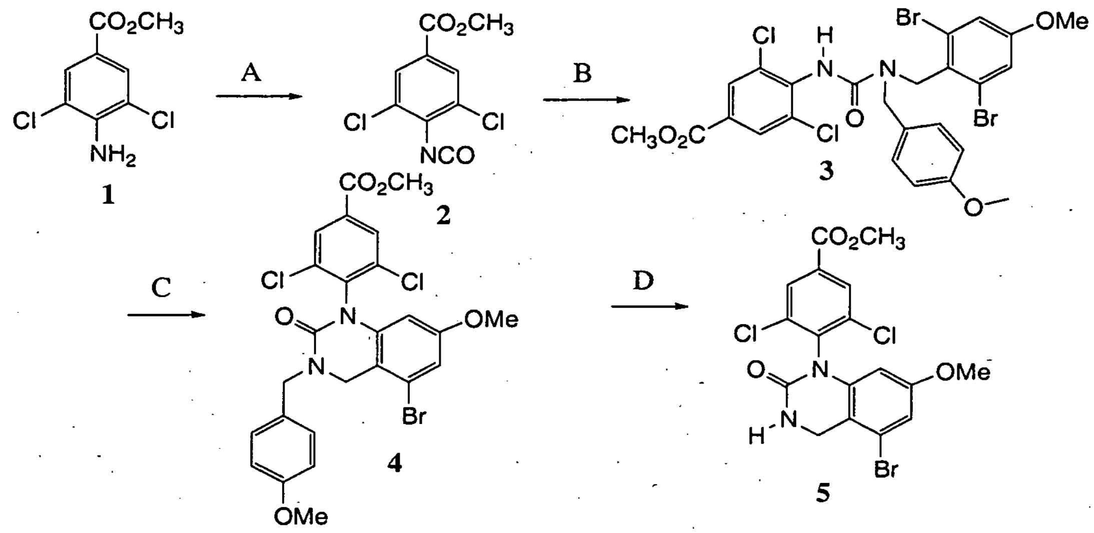
A solution of 5.9g of 6-(2,4-difluorophenyl)-5-methyl-2-(methylthio)pyrimidin-4-ol in 25mL of $POCl_3$ was heated to reflux and stirred at this temperature for 5h. All but *ca.* 5mL of $POCl_3$ was removed by vacuum distillation, and the residue was quenched by pouring into 200 mL of ice-water, neutralizing with Na_2CO_3 and extracting with 3 x 100mL of EtOAc. The combined organics were washed with 100mL of brine, dried, and concentrated. The residue was purified by flash chromatography on a Biotage 40M column, eluting with 95:5 hexanes-acetone to yield the title compound as a light yellow solid. Mass spectrum (ESI) 287 (M+1).

Step D: 5-(bromomethyl)-4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidine

A suspension of 5.4g of 4-chloro-6-(2,4-difluorophenyl)-5-methyl-2-(methylthio)pyrimidine. 3.69g of *N*-bromosuccinimide, and 460mg of benzoyl peroxide in 75mL of CCl_4 was heated to reflux and stirred at this temperature for 6h, then cooled in the freezer for 1h. The solids were filtered and washed liberally with cold CCl_4, and the filtrate was concentrated. The residue was purified by flash chromatography on a Biotage 40M column, eluting with a gradient system of 99:1 to 97:3 hexanes-acetone to yield the title compound. Mass spectrum (ESI) 367 (M+1).

COMPOUND PPP-1

1-(2,6-dichloro-4-carbomethoxyphenyl)- 5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone



Step A: 2,6-Dichloro-4-Carbomethyoxyphenylisocyanate

A mixture of 10.95g (50mmol) of methyl 4-amino-3,5-dichlorobenzoate and 50mL of a 2M solution of phosgene in toluene was sealed and heated at 110°C for 18h. After cooling to rt, the solution was concentrated under vacuum and solid residue was dried under high vacuum for 48h to afford **2** as a white solid. Mass spectrum (ESI), 246 (M+1), 248 (M+3).

Step B: N-[(2,6-dibromo-4-methoxyphenyl)methyl]-N'-(2,6-dichloro-4-carbomethoxyphenyl)-N-[(4-methoxyphenyl)methyl]urea

Compound **2** was converted to **3** by reaction with **INTERMEDIATE 20** under the conditions described for preparation of **INTERMEDIATE 21**. Mass spectrum (ESI), 659 (M+1), 661 (M+3), 663 (M+5), 665 (M+7).

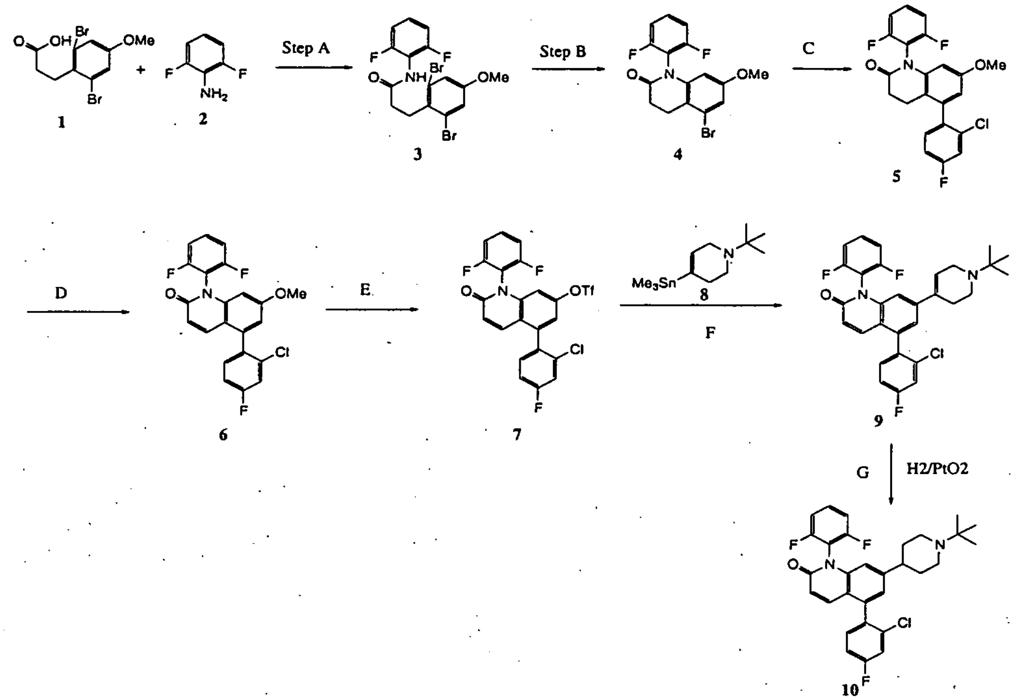
Step C: 1-(2,6-dichloro-4-carbomethoxyphenyl)-3-(4-methoxyphenyl)methyl-5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

Compound **3** was converted to **4** using the conditions described for preparation of **INTERMEDIATE 22**. Mass spectrum (ESI), 521 (M+1), 523 (M+3), 525 (M+5).

Step D: 1-(2,6-dichloro-4-carbomethoxyphenyl)- 5-bromo-7-methoxy-3,4-dihydro-2(1H)-quinazolinone

Compound **4** was converted to **5** using the conditions described for preparation of **INTERMEDIATE 23**. Mass Spectrum (ESI), 401 (M+1), 403 (M+3), 405 (M+5)

EXAMPLE PPP1



Step A: A solution of **1** (0.5132mg, 1.52mmol), in 20mL of CH_2Cl_2 was added oxalyl bromide (0.84mL as 2M solution) at -78^oC and the DMF (0.91mmol, 0.071mL). The solution was allowed to warmed to rt for 1h and ethyl diisopropyl amine (1.82mmol, 0.318mL) and 2,6-difluoroaniline (1.52mmol, 0.164mL) was added. The solution was stirred at rt for 4h and white solid was collected by filtering as **3**.

Step B: Compound **1** (5.16g, 11.5mmol), K_2CO_3 (4.76g, 34.5 mmol) and CuI (1.44mmol, 7.6mmol) in 115mL of DMF was heated at 140^oC for 2.2h and DMF was removed by vacuum. The residue was dissolved in EtOAc and the solution was washed with brine, dried with Na_2SO_4 and filtered through celite. Upon removal of solvent, the residue was purified by EtOAc/Hex = 1:4 to give **4** as a solid. Mass spectrum (ESI) 368 (M+1).

Step C: A solution of **4** (1.02g, 2.76 mmol), 2-Cl-4-F boronic acid (0.77g, 4.42mmol), Pd(PPh3)4 (0.16g, 0.14mmol) and Na_2CO_3 (4.42mmol, as 2M solotion) in 5mL of toluene was added EtOH (5mL) and water (2mL). The solution was purged with N_2 and was heated to 102^oC for 6h. It was then poured into ether and washed with $NaHCO_3$ (1x), brine (1x), and dried with Na_2SO_4. The residue was purified by EtOAc/Hex = 1:6 to 1:4 to give **5** as a solid. Mass spectrum (ESI) 418 (M+1).

Step D: A solution of **5** (1.12g, 2.68mmol), NBS (0.50g, 2.81mmol) and benzoyl peroxide (0.071g, 0.29mmol) in 60mL of CCl_4 was heated to reflux under IR lamp for 30min. Solvent was removed and the residue was purified by flash

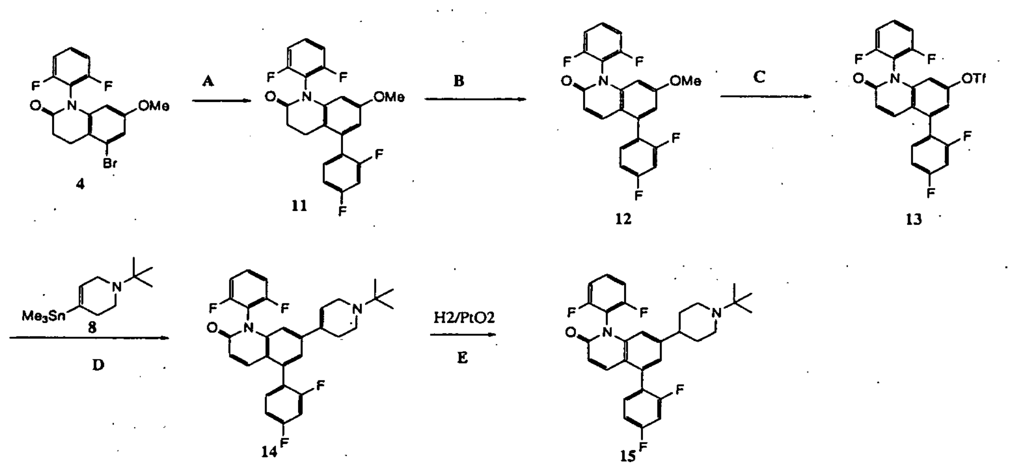
chromatography with EtOAc/hex = 1:3 to give **6**. Mass spectrum (ESI) for **6**, 416 (M+1).

Step E: A solution of **6** (1.10g, 2.68mmol) in 16mL of CH_2Cl_2 was added BBr_3 (10.7mmol, as 1M solution) and was stirred at rt for 4h. It was poured in EtOAc and washed with pH = 7 buffer solution. The organic layer was dried with Na_2SO_4, filtered and concentrated to give a white solid. The solid was dissolved in 30mL of CH_2Cl_2 and was added Et_3N (1.49mL) and 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (1.58g, 4.02mmol). After 40min, volatiles were removed and the residue was purified by flash chromatography with EtOAc/hex = 1:4 to give **7**. Mass spectrum (ESI) for **7**, 534 (M+1).

Step F: A solution of **7** (0.912g, 1.71mmol), **8** (0.72g, 2.39mmol), LiCl (0.29g, 6.84mmol) and $Pd(PPh_3)_4$ (0.20g, 0.17mmol) in 30mL of 1,4-dioxane was heated at 108^oC under N_2 for 20h. Upon removal of solvent, it was dissolved in EtOAc and was washed with $NaHCO_3$ (1x). The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography with Hex/EtOAc/2N NH_3 in MeOH = 100:10:2 give **9**. Mass spectrum (ESI) for **9**, 523(M+1).

Step G: A solution of **9** (0.674g, 1.20mmol as HCl salt) in 20mL of EtOAc was added 2.5mL of MeOH and PtO_2 (0.27g). The solution was hydrogenated on Parr shaker at 3psi for 20min and was added 4mL of 2N NH_3 in MeOH. The mixture was filtered through Celite and the residue was purified by flash chromatography with Hex/EtOAc/2N NH_3 in MeOH = 100:10:2 give **10 (EXAMPLE PPP1)**. Mass spectrum (ESI) for **10**, 525 (M+1).

EXAMPLE PPP2



Step A: The compound **11** was prepared as described in **Step C** of **EXAMPLE PPP1** except that 2,4-difluorophenylboronic acid was used instead of 2-chloro-4-fluorophenylboronic acid. Mass spectrum (ESI), 402 (M+1).

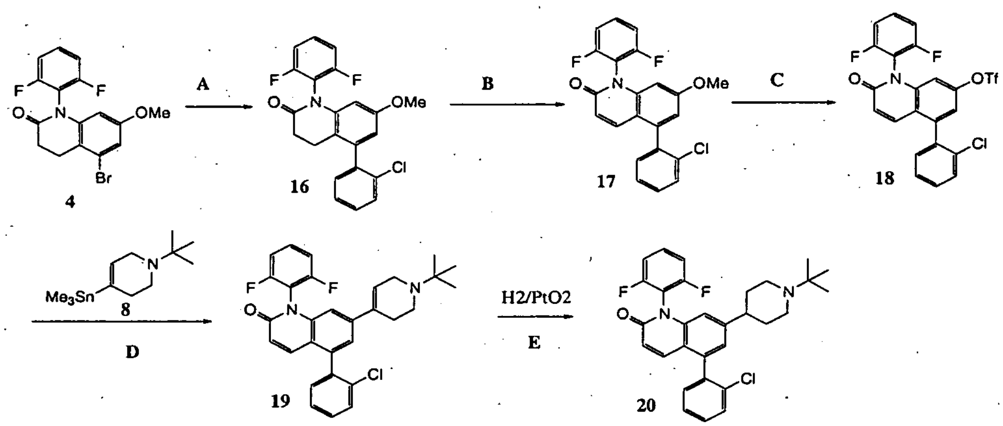
Step B: Compound **11** was converted to **12** using the conditions described in **Step D** of **EXAMPLE PPP1**. Mass spectrum (ESI), 400 (M+1).

Step C: Compound **12** was converted to **13** using the conditions described in **Step E** of **EXAMPLE PPP1**. Mass spectrum (ESI), 518 (M+1).

Step D: Compound **13** was converted to **14** using the conditions described in **Step F** of **EXAMPLE PPP1**. Mass Spectrum (ESI), 507 (M+1)

Step E: Compound **14** was converted to **15 (EXAMPLE PPP2)** using the conditions described in **Step G** of **EXAMPLE PPP1**. Mass Spectrum (ESI), 509 (M+1)

EXAMPLE PPP3



Step A: The compound **16** was prepared as described in **Step C** of **EXAMPLE PPP1** except that 2-chlorophenylboronic acid was used instead of 2-chloro-4-fluorophenylboronic acid. Mass spectrum (ESI), 400 (M+1).

Step B: Compound **16** was converted to **17** using the conditions described in **Step D** of **EXAMPLE PPP1**. Mass spectrum (ESI), 398 (M+1).

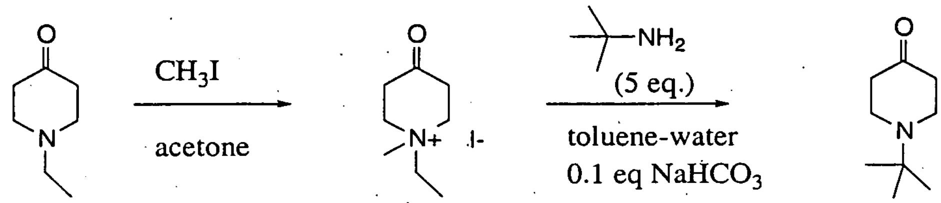
Step C: Compound **17** was converted to **18** using the conditions described in **Step E** of **EXAMPLE PPP1**. Mass spectrum (ESI), 516 (M+1).

Step D: Compound **18** was converted to **19** using the conditions described in **Step F** of **EXAMPLE PPP1**. Mass Spectrum (ESI), 505 (M+1)

Step E: Compound **19** was converted to **20 (EXAMPLE PPP3)** using the conditions described in **Step G** of **EXAMPLE PPP1**. Mass Spectrum (ESI), 507 (M+1)

COMPOUND PPA-1

1-tert-Butyl-4-Oxopiperidine



Step A: 1-Ethyl-1-Methyl-4-Oxopiperidinium Iodide

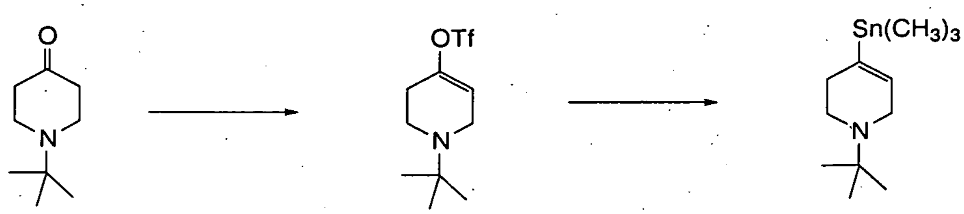
A solution of 100g (0.789mol) of 1-ethyl-4-oxopiperidine in 1000mL of acetone was stirred at rt in a water bath. To this was added 62.2mL (142g, 1mol) of methyl iodide, dropwise at such a rate to keep the temperature below 30 degrees. A precipitate developed within minutes and the mixture was stirred at rt for 4h. The mixture was filtered and the precipitate washed with acetone and dried to afford the title compound as a white solid. Mass spectrum (ESI) 142 (M+).

Step B 1-tert-Butyl-4-Oxopiperidine

To a solution of 137mL (1.3moles) of tert-butylamine in 700mL of toluene was added solution of 70g (0.260moles) of 1-ethyl-1-methyl-4-oxopiperidinium iodide and 2.18g (0.026moles) of $NaHCO_3$ in 100mL of water. The mixture was stirred at 78°C for 6h. After it had cooled to rt, the layers were separated and the aq layer was washed with three 200mL portions of ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to an oil that purified by distillation under reduced pressure. Fractions distilling at 72°C at 3mm were collected to afford the title compound as a colorless liquid. ^1H NMR($CDCl_3$, 500MHz): δ 1.15 (s, 9H), 2.45 (t, 4H, J = 6.1 Hz), 2.86 (t, 4H, J = 6.1H); Mass spectrum (ESI) 156 (M+1).

COMPOUND PPA-2

1-*tert*-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine



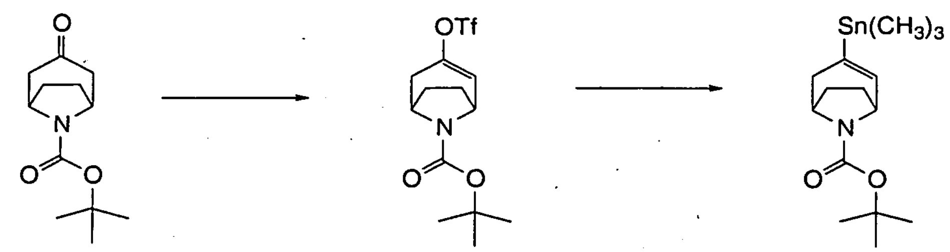
Step A: 1-tert-Butyl-4-Trifluoromethanesulfonlyoxy-1, 2, 3, 6-tetrahydropyridine

A solution of 8.0g (52mmol) of 1-tert-butyl-4-oxo-piperidine in 60mL of anhydrous tetrahydrofuran was cooled to –78°C under N_2. To this was added 72mL of a 1M solution of lithium hexamethyldisilamide. The solution was stirred at –78°C for 10min, warmed to 0°C for 30min, and then re-cooled to –78°C. To this was added 28.3g (72mmol) of 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine and the solution was stirred at –30°C for 2h. The reaction was quenched by addition of 10mL saturated $NaHCO_3$ and the solution was concentrated under vacuum. The residue was dissolved in 200mL ether, washed with 50mL portions of saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. That residue was applied to a Biotage 65 silica gel column that had been pre-treated with 30mL triethylamine before equilibration with ethyl acetate-hexane-triethylamine, 500:50:1. The column was eluted with the same mixture and homogeneous fractions were pooled and concentrated to give the title compound as a colorless liquid. ^{1}H NMR($CDCl_3$, 500MHz): δ 1.154(s, 9H), 2.45 (m, 2H), 2.78 (t, 2H, J = 5.4H), 3.28 (m, 2H), 5.76 (m, 1H).

Step B: 1-*tert*-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine

A solution of 10.36g (36.1mmol) of 1-tert-butyl-4-trifluoromethanesulfonlyoxy-1, 2, 3, 6-tetrahydropyridine, 15.4g (46.9mmol) of hexamethylditin, 6.1g (145mmol) of LiCl, and 2.1g (1.8mmol) tetrakis(triphenylphosphine)palladium in 120mL of anhydrous THF was purged with Ar. After 15min, the mixture was heated at reflux (84°C) for 4h. The black solution was diluted with 300mL ether and washed with saturated $KHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated. That residue was applied to a Biotage 65 silica gel column that had been pre-treated with 30mL triethylamine before equilibration with ethyl acetate-hexane-triethylamine, 500:50:1. The column was eluted with the same mixture and homogeneous fractions were pooled and concentrated to give the title compound as a pale yellow liquid. ^{1}H NMR($CDCl_3$, 500MHz): δ 0.06-0.16 (m, 9H), 1.11(s, 9H), 2.35 (m, 2H), 2.64 (t, 2H, J = 5.5H), 3.20 (m, 2H), 5.85 (m, 1H).

COMPOUND PPA-3



Step A: <u>8-t-Butoxycarbonyl-3-(trifluoromethansulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene</u>

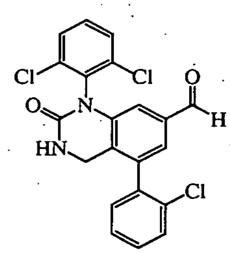
The N-t-butoxycarobonylnortropanone was converted to the corresponding triflate using the conditions described in **Part A** of **COMPOUND PPA-2.** ^{1}H NMR($CDCl_3$, 500MHz): δ 1.15(s, 9H), 1.75 (m, 1H), 1.99-2.3 (m, 4H), 2.9-3.2 (m, 1H), 4.48 (m, 2H), 6.11 (s, 1H).

Step B: <u>8-t-Butoxycarbonyl-3-(trimethylstannyl)-8-azabicyclo[3.2.1]oct-2-ene</u>

The 8-t-Butoxycarbonyl-3-(trifluoromethansulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene was converted to the corresponding trimethylstannyl analog using the conditions described in **Part B** of **COMPOUND PPA-2.** ^{1}H NMR($CDCl_3$, 500MHz): δ 0.06-0.16 (m, 9H), 1.47(s, 9H), 1.68 (m, 1H), 1.87-2.0 (m, 3H), 2.18 (m, 1H), 2.8-3.0 (m, 1H), 4.19-3.32 (m, 2H), 6.14 (m, 1H).

INTERMEDIATE AAA1

<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde</u>



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3,4-dihydroquinazolin-2(1*H*)-one

To a stirred solution of methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**INTERMEDIATE 32**) (8.23g) in THF (140mL) was added lithium aluminum hydride (14mL of a 1.0M solution in THF) and the mixture was let stir 1.5h. More lithium aluminum hydride (4.5mL of a 1.0M solution in THF) was added and the

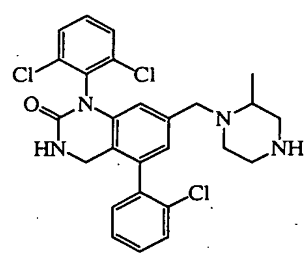
mixture was stirred overnight. Another portion of lithium aluminum hydride (4.5mL of a 1.0M solution in THF) was added and stirred 4h. The reaction was carefully poured into a flask containing 1N aqueous HCl (500mL) and stirred. To the mixture was added ethyl acetate (500mL) and the layers were mixed, then separated. The organic layer was washed with brine (300mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting solid was triturated with hexanes, then CH_2Cl_2 to give the 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3,4-dihydroquinazolin-2(1*H*)-one compound.

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde

To a suspension of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3,4-dihydroquinazolin-2(1*H*)-one (780mg, 1.8mmol) in methylene chloride (15mL) was added 4-methylmorpholine N-oxide (316mg, 2.7mmol). To the resulting clear solution was added molecular sieves (900mg) followed by tetrapropylammonium perruthenate (32mg, 0.09mmol). The resulting mixture was stirred at rt for 2h. The mixture was then filtered through silica gel eluting with ethyl acetate. Removal of the solvent and subsequent purification by flash chromatography using 25% acetone/hexane provided 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.43 (abq, 2H, J = 15.5 Hz), 5.37 (s, 1H), 6.66 (s, 1H), 7.30-7.60 (m, 8H), 9.85 (s, 1).

EXAMPLE AAA1

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-3-methylpiperazine-1-carboxylate

A solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (Intermediate AAA1, 208mg,

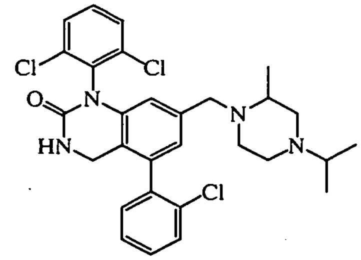
0.48mmol) and 1-BOC-3-methylpiperazine (96mg, 0.48mmol) in dichloroethane (5mL) was stirred at rt for 30 min. To this was added sodium triacetoxyborohydride (150mg, 0.67mmol) followed by acetic acid (29mg, 0.48mmol). The resulting reaction mixture was stirred at rt for 20h. The reaction was quenched with 2N NaOH solution (6mL) followed by extraction with ethyl acetate (100mL x 2). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by flash chromatography using 25% acetone/hexane provided *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-3-methylpiperazine-1-carboxylate as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (s, 3H), 1.46 (s, 9H), 2.06 (brs, 1H), 2.39 (brs, 1H), 2.60 (brs, 1H), 2.82 (brs, 1H), 3.05 (brs, 1H), 3.15 (m, 1H), 3.54 (brs, 2H), 3.82 (brs, 1H), 4.34 (abq, 2H, J = 14.2Hz), 5.15 (s, 1H), 6.16 (d, 1H, J = 5.2 Hz), 6.88 (s, 1H), 7.20-7.60 (m, 7H). MS (API-ES+): 617 (M+H).

STEP B: <u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one</u>

To a solution of *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-3-methylpiperazine-1-carboxylate (186mg, 0.30mmol) in methylene chloride (1mL) at 0°C was added trifluoroacetic acid (0.92mL) dropwise. Then the reaction was stirred at rt for 1h. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 8% of 2N ammonium in methanol/methylene chloride as eluent provided the 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one compound. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (m, 3H), 2.06 (m, 2H), 2.32 (s, 1H), 2.48 (m, 1H), 2.63 (m, 1H), 2.72 (t, 1H, J = 10.2 Hz), 2.84 (m, 2H), 3.15 (dd, 1H, J_1 = 14.0 Hz, J_2 = 6.0 Hz), 3.86 (t, 1H, J = 13.2 Hz), 4.34 (abq, 2H, J = 14.2Hz), 5.23 (s, 1H), 6.15 (d, 1H, J = 9.4 Hz), 6.88 (s, 1H), 7.20-7.60 (m, 7H). MS (API-ES+): 517 (M+H).

EXAMPLE AAA2

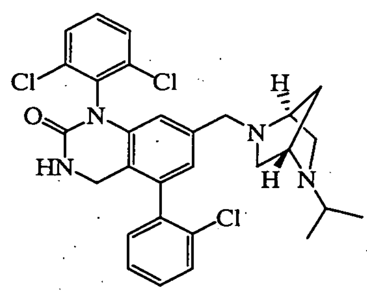
<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropyl-2-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one</u>



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA1**) and acetone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (s, 9H), 1.40 (brs, 1H), 1.60 (brs, 1H), 2.20 (brs, 2H), 2.40 (brs, 1H), 2.65 (brs, 3H), 3.15 (brs, 1H), 3.90 (brs, 1H), 4.34 (abq, 2H, J = 14.4 Hz), 5.00 (s, 1H), 6.13 (brs, 1H), 6.89 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 559 (M+H).

EXAMPLE AAA3

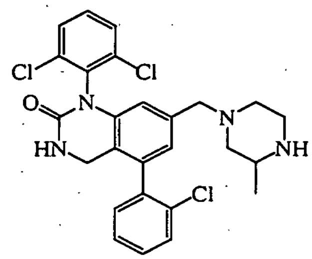
<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[(1*S*,4*S*)-5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl}-3,4-dihydroquinazolin-2(1*H*)-one</u>



The title compound was prepared from 5-(2-chlorophenyl)-7-[(1*R*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1H)-one (**EXAMPLE 66**) and acetone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (m, 6H), 2.42 (m, 2H), 2.57 (brs, 1H), 2.86 (brs, 2H), 3.17 (brs, 1H), 3.55 (t, 2H, J = 13.5 Hz), 3.66 (t, 1H, J = 13.5 Hz), 4.34 (abq, 2H, J = 14.4 Hz), 5.04 (s, 1H), 6.24 (s, 1H), 6.87 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 557 (M+H).

EXAMPLE AAA4

<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one</u>



STEP A: benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-2-methylpiperazine-1-carboxylate

The benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-2-methylpiperazine-1-carboxylate was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 1-CBz-2-methylpiperazine as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.08 (d, 3H, J = 5.9 Hz), 2.00 (m, 1H), 2.10 (m, 1H), 2.52 (d, 1H, J = 11.0 Hz), 2.70 (m, 1H), 3.06 (m, 1H), 3.26 (m, 1H), 3.46 (m, 1H), 3.86 (d, 1H, J = 12.5 Hz), 4.2-4.5 (m, 3H), 5.05 (s, 1H), 5.14 (abq, 2H, J = 12.4 Hz), 6.25 (d, 1H, J = 13.3 Hz), 6.82 (s, 1H), 7.30-7.60 (m, 12H). MS (API-ES+): 651 (M+H).

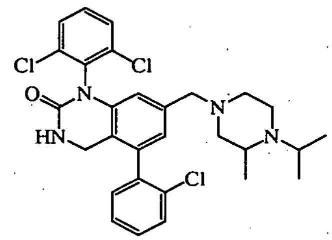
STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one

To a solution of benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-2-methylpiperazine-1-carboxylate (105mg, 0.16mmol) in methylene chloride (2mL) at 0°C was added 30% HBr/HOAc (0.32mL, 1.62mmol) slowly. The resulting reaction mixture was stirred at 0°C for 30min, and then at rt for 30min. The reaction was quenched with water, then added 5N NaOH solution to pH ~1, and extracted with methylene chloride (50mL x 3) and ethyl acetate (50mL x 2). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 8% of 2N ammonium in methanol/methylene chloride as eluent provided 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (d, 3H, J = 4.8 Hz), 1.72 (m, 1H), 2.06 (m, 1H), 2.69 (m, 2H), 2.82 (t, 2H, J = 9.3 Hz), 2.98 (d, 1H, J = 11.9 Hz),

3.40 (m, 2H), 4.34 (abq, 2H, J = 14.4 Hz), 5.10 (s, 1H), 6.17 (s, 1H), 6.84 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 517 (M+H).

EXAMPLE AAA5

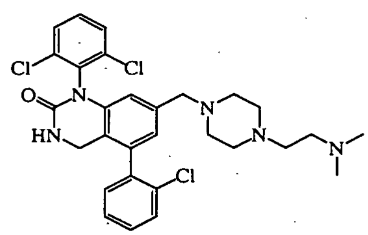
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropyl-3-methylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA 1**) and 1-isopropyl-2-methylpiperazine as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (brs, 3H), 0.93 (brs, 3H), 0.98 (brs, 3H), 1.92 (brs, 1H), 2.16 (brs, 1H), 2.31 (brs, 1H), 2.57 (m, 2H), 2.67 (brs, 1H), 3.21 (brs, 1H), 3.40 (s, 2H), 4.22-4.485 (m, 2H), 5.05 (s, 1H), 6.17 (s, 1H), 6.85 (d, 1H, J = 3.7 Hz), 7.30-7.60 (m, 7H). MS (API-ES+): 559 (M+H).

EXAMPLE AAA6

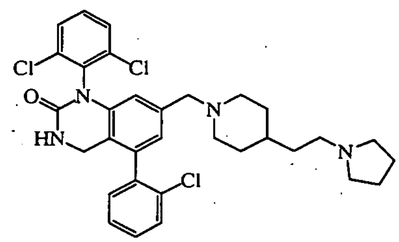
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}methyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 1-(2-dimethylaminoethyl)-piperazine as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 6H), 2.46 (m, 12H), 3.40 (abq, 2H, J = 14.0 Hz), 4.34 (abq, 2H, J = 14.4 Hz), 5.06 (s, 1H), 6.15 (s, 1H), 6.86 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 574 (M+H).

EXAMPLE AAA7

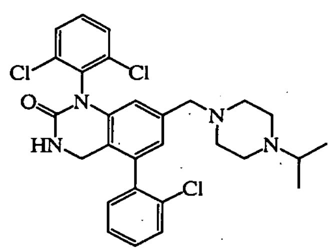
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[4-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]methyl}-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 4-(2-pyrrolidinoethyl)-piperidin as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18 (m, 2H), 1.28 (m, 1H), 1.61 (m, 6H), 1.88 (m, 6H), 2.56 (brs, 4H), 2.76 (m, 2H), 3.38 (s, 2H), 4.34 (abq, 2H, J = 14.4 Hz), 4.98 (s, 1H), 6.15 (s, 1H), 6.86 (s, 1H), 7.30-7.58 (m, 7H). MS (API-ES+): 599 (M+H).

EXAMPLE AAA8

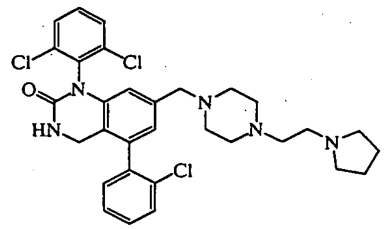
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 1-isopropylpiperazine as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (s, 6H), 2.48 (brs, 8H), 2. 65 (brs, 1H), 3.41 (abq, 2H, J = 13.9 Hz), 4.34 (abq, 2H, J = 14.4 Hz), 5.08 (s, 1H), 6.16 (s, 1H), 6.87 (s, 1H), 7.30-7.56 (m, 7H). MS (API-ES+): 545 (M+H).

EXAMPLE AAA9

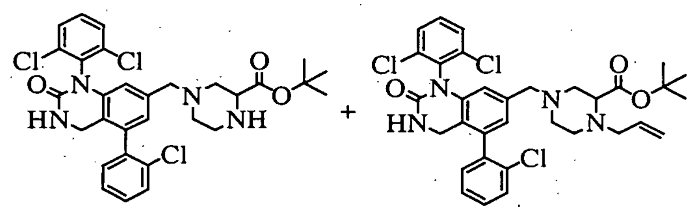
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]methyl}-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 1-(2-pyrrolidinoethyl)-piperazine as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.81 (s, 4H), 2.42 (brs, 8H), 2.56 (m, 6H), 2.64 (m, 2H), 3.40 (abq, 2H, J = 13.7 Hz), 4.34 (abq, 2H, J = 14.4 Hz), 5.14 (s, 1H), 6.16 (s, 1H), 6.86 (s, 1H), 7.29-7.56 (m, 7H). MS (API-ES+): 598 (M+H).

EXAMPLE AAA10 and EXAMPLE AAA10A

tert-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate and *tert*-butyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate



STEP A: 1-allyl 2-*tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-1,2-dicarboxylate

The 1-allyl 2-*tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-1,2-dicarboxylate was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**INTERMEDIATE AAA1**) and 1-allyloxycarbonyl-2-*t*-butyloxycarbonyl piperazine as described in **EXAMPLE AAA1,**

STEP A. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34 (s, 9H), 1.92 (m, 1H), 2.26 (m, 1H), 2.70 (m, 1H), 3.12 (m, 1H), 3.30 (m, 3H), 3.50 (m, 1H), 3.83 (m, 1H), 4.34 (abq, 2H, J = 14.4 Hz), 4.54 (m, 1H), 4.62 (brs, 2H), 5.03 (s, 1H), 5.16-5.36 (m, 2H), 5.93 (brs, 1H), 6.11 (s, 1H), 6.85 (d, 1H, J = 10.1 Hz), 7.32-7.56 (m, 7H). MS (API-ES+): 687 (M+H).

STEP B: *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate and *tert*-butyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate

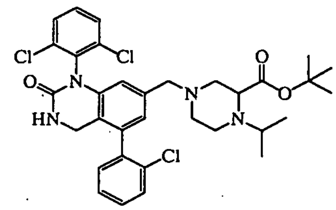
To a mixture of 1-allyl 2-*tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-1,2-dicarboxylate (**EXAMPLE AAA10, STEP A**, 200mg, 0.29mmol) and dichlorobis(triphenylphosphine)palladium(II) (10.2mg, 0.0146mL) in methylene chloride (3mL) was added water (30μL). To this mixture was added tributyltin hydride (94μL, 0.348mmol) rapidly. The mixture was stirred at rt for 5h, diluted with methylene chloride, washed with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 5% of 2N ammonium in methanol/methylene chloride as eluent provided *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate and *tert*-butyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate.

tert-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.43 (s, 9H), 2.10 (m, 1H), 2.22 (m, 1H), 2.52 (m, 1H), 2.73 (m, 1H), 2.88 (m, 1H), 3.37 (m, 1H), 3.43 (s, 2H), 4.34 (d of abq, 2H, J_1 = 14.4 Hz, J_2 = 6.8 Hz), 5.03 (s, 1H), 6.17 (d, 1H, J = 6.4 Hz), 6.85 (d, 1H, J = 9.4 Hz), 7.30-7.56 (m, 7H). MS (API-ES+): 603 (M+H).

EXAMPLE AAA10A: *tert*-butyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (s, 9H), 2.27 (m, 1H), 2.40 (m, 2H), 2.54 (m, 1H), 2.64 (m, 1H), 3.02 (m, 3H), 3.37 (m, 3H), 4.25 (dd, 1H, J_1 = 14.4 Hz, J_2 = 5.7 Hz), 4.43 (dd, 1H, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 5.05 (s, 1H), 5.16 (m, 2H), 5.86 (m, 1H), 6.13 (s, 1H), 6.86 (d, 1H, J = 5.9 Hz), 7.28-7.58 (m, 7H). MS (API-ES+): 643 (M+H).

EXAMPLE AAA11

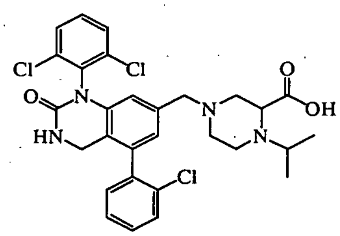
tert-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-1-isopropylpiperazine-2-carboxylate



The title compound was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate (**EXAMPLE AAA10**) and acetone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.96 (d, 3H, J = 6.2 Hz), 1.11 (d, 3H, J = 6.4 Hz), 1.41 (s, 9H), 2.42 (m, 3H), 2.53 (m, 1H), 2.62 (m, 1H), 2.86 (m, 1H), 3.03 (m, 1H), 3.28 (m, 1H), 3.38 (m, 2H), 4.25 (dd, 1H, J_1 = 14.4 Hz, J_2 = 5.3 Hz), 4.44 (dd, 1H, J_1 = 14.4 Hz, J_2 = 8.2 Hz), 5.00 (s, 1H), 6.15 (s, 1H), 6.85 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 645 (M+H).

EXAMPLE AAA12

4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-1-isopropylpiperazine-2-carboxylic acid

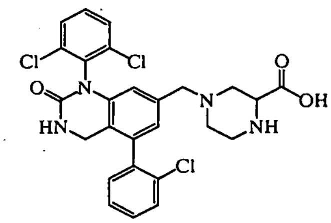


To the solution of *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}-1-isopropylpiperazine-2-carboxylate (**EXAMPLE AAA11**, 30mg, 0.047mmol) in trifluoroacetic acid (0.6mL) was added water (0.03mL). The reaction was stirred at rt for 20h. Removal of the solvent and subsequent addition of ether resulted in a white precipitate. Filtration of the precipitate followed by washing with ether provided the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.22 (d, 3H, J = 7.0 Hz), 1.24 (d, 3H, J = 6.9 Hz), 3.12(m, 2H), 3.30 (m, 1H), 3.44 (m, 1H), 3.50 (abq, 2H, J = 7.1 Hz),

3.74 (m, 1H), 3.81 (m, 1H), 3.96 (m, 1H), 4.07 (m, 1H), 4.28 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz), 4.42 (dd, 1H, J_1 = 14.9 Hz, J_2 = 10.1 Hz), 5.80 (brs, 1H), 6.13 (d, 1H, J = 9.8 Hz), 6.95 (s, 1H), 7.32-7.58 (m, 7H). MS (API-ES+): 589 (M+H).

EXAMPLE AAA13

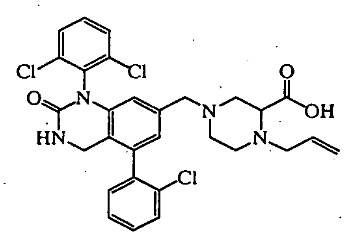
4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylic acid



The title compound was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate (**EXAMPLE AAA10**) as described in **EXAMPLE AAA12.** ^{1}H NMR (DMSO, 500 MHz): δ 2.30 (m, 1H), 2.40 (m, 1H), 2.63 (m, 1H), 2.93 (m, 2H), 3.18 (m, 1H), 3.49 (s, 2H), 4.00 (m, 1H), 4.10 (m, 2H), 6.00 (s, 1H), 6.83 (d, 1H, J = 6.4 Hz), 7.30-7.72 (m, 8H), 9.05 (brs, 2H). MS (API-ES+): 547 (M+H).

EXAMPLE AAA14

1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylic acid

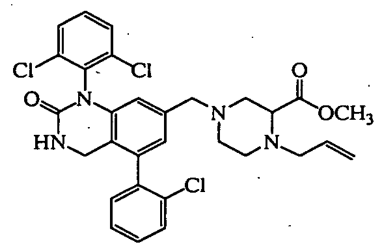


The title compound was prepared from *tert*-butyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate (**EXAMPLE AAA10**) as described in **EXAMPLE AAA12.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.98 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 3.76 (m, 3H), 4.13 (m, 1H), 4.28 (m, 1H), 4.43 (m, 1H), 5.36 (m, 2H),

5.66 (s, 1H), 5.81 (m, 1H), 6.10 (d, 1H, J = 5.5 Hz), 6.93 (d, 1H, J = 6.7 Hz), 7.30-7.60 (m, 7H). MS (API-ES+): 586 (M+H).

EXAMPLE AAA15

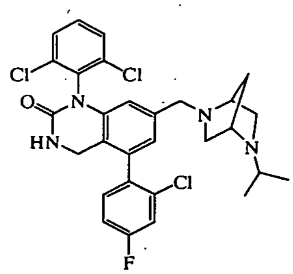
Methyl 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylate



A mixture of 1-allyl-4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperazine-2-carboxylic acid (**EXAMPLE AAA14**, 95mg, 0.16mmol), methanol (0.02mL, 0.49mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (47mg, 0.24mmol) and 4-(dimethylamino)-pyridine (50mg, 0.41mmol) in methylene chloride (1mL) was stirred at rt for 20 h. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 5% of 2N ammonium in methanol/methylene chloride as eluent provided the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.31 (brs, 1H), 2.42 (m, 1H), 2.47 (m, 1H), 2.56 (m, 1H), 2.64 (m, 1H), 3.02 brs, 2H), 3.20 (brs, 1H), 3.32 (m, 1H), 3.42 (m, 2H), 3.65 (s, 3H), 4.25 (dd, 1H, J_1 = 14.2 Hz, J_2 = 6.2 Hz), 4.43 (dd, 1H, J_1 = 14.4 Hz, J_2 = 8.0 Hz), 5.06 (s, 1H), 5.16 (s, 2H), 5.84 (m, 1H), 6.11 (d, 1H, J = 13.3 Hz), 6.83 (d, 1H, J = 3.2Hz), 7.30-7.60 (m, 7H). MS (API-ES+): 601 (M+H).

EXAMPLE AAA16

5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-bromo-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one:

To a solution of methyl 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**INTERMEDIATE 27**)(2g, 3.63mmol) in anhydrous THF at 0°C was added lithium aluminum hydride (1.0M in THF, 4.7mL, 4.73mmol) slowly. The reaction was stirred at 0°C for 40min, quenched with water slowly and diluted with methylene chloride. The mixture was filtered through celite and rinsed with methylene chloride. Removal of the solvent and subsequent purification by flash chromatography using 20% of acetone in hexane as eluent provided the 5-bromo-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (s, 3H), 4.49 (s, 2H), 4.50 (s, 2H), 4.69 (s, 2H), 5.98 (s, 1H), 6.92 (d, 2H, J = 8.5 Hz), 7.23 (s, 1H), 7.36 (m, 3H), 7.52 (d, 2H, J = 8.0 Hz). MS (API-ES+): 523 (M+H).

STEP B: 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde:

The 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde was prepared from 5-bromo-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA16, STEP A**) as described in **INTERMEDIATE AAA1**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.84 (s, 3H), 4.56 (s, 2H), 4.70 (s, 2H), 6.47 (s, 1H), 6.93 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.0 Hz), 7.69 (s, 1H), 9.75 (s, 1H).

STEP C: 5-bromo-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 5-bromo-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde (**EXAMPLE AAA16, STEP B**) and 2-isopropyl-2,5-diazabicyclo[2.2.1]heptane (**INTERMEDIATE ABA2**) as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 (brs, 3H), 1.22 (brs, 3H), 1.74 (brs, 1H), 1.90 (brs, 1H), 243 (brs, 2H), 2.72 (brs, 1H), 2.88 (brs, 1H), 3.07 (brs, 1H), 3.16 (s, 2H), 3.53 (abq, 2H, J = 14.2 Hz), 3.72 (brs, 1H), 3.83 (s, 3H), 4.48 (s, 2H), 4.68 (s, 2H), 6.05 (s, 1H), 6.91 (d, 2H, J = 8.5 Hz),

7.17 (s, 1H), 7.36 (d, 2H, J = 8.4 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz). MS (API-ES+): 645 (M+H).

STEP D: 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

To a solution of 5-bromo-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (200mg, 0.31mmol) and 2-chloro-4-fluoro-benzene boronic acid (98mg, 0.62mmol) in toluene (3mL) and ethanol (0.3mL) was added sodium carbonate (2M solution, 0.39mL) and tetrakis(triphenylphosphine) palladium (0) (18mg, 0.0155mmol). The flask was evacuated and purged with nitrogen a few times. The reaction mixture was heated to reflux for 2h and diluted with methylene chloride. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 5% of 2N ammonium in methanol/methylene chloride as eluent provided the 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.03 (s, 3H), 1.08 (s, 3H), 1.64 (m, 2H), 2.40 (m, 1H), 2.57 (brs, 1H), 2.83 (t, 1H, J = 7.3 Hz), 2.90 (brs, 1H), 3.14 (s, 1H), 3.53 (m, 2H), 3.63 (t, 1H, J = 13.2 Hz), 3.81 (s, 3H), 4.11 (abq, 2H, J = 14.9 Hz), 4.55 (abq, 2H, J = 14.9 Hz), 6.22 (s, 1H), 6.78 (s, 1H), 6.84 (d, 2H, J = 8.4 Hz), 6.99 (t, 1H, J = 8.0 Hz), 7.12 (dd, 1H, J_1 = 8.4 Hz, J_2 = 6.0 Hz), 7.21 (d, 3H, J = 8.7 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.54 (m, 2H). MS (API-ES+): 695 (M+H).

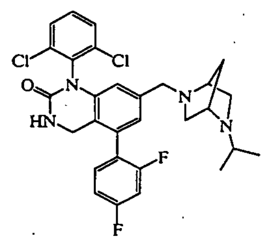
STEP E: 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one

The solution of 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (136mg, 0.20mmol) in trifluoroacetic acid (1.5mL) was stirred at 60°C for 1h. It was cooled to rt and treated with 5N NaOH solution to pH 9~10. The resulting mixture was extracted with methylene chloride. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by preparative thin layer chromatography using 8% of 2N ammonium in methanol/methylene chloride as eluent provided the 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.03 (d, 3H, J = 5.7 Hz), 1.08 (d, 3H, J = 5.7

Hz), 1.66 (m, 2H), 2.37 (t, 1H, J = 8.2 Hz), 2.43 (t, 1H, J = 11.9 Hz), 2.56 (brs, 1H), 2.83 (t, 1H, J = 9.2 Hz), 2.90 (d, 1H, J = 8.7 Hz), 3.14 (s, 1H), 3.54 (m, 2H), 3.64 (t, 1H, J = 13.0 Hz), 4.33 (abq, 2H, J = 14.2 Hz), 5.12 (s, 1H), 6.24 (s, 1H), 6.84 (s, 1H), 7.08 (t, 1H, J = 8.0 Hz), 7.28 (m, 2H), 7.39 (d, 1H, J = 8.0 Hz), 7.54 (t, 1H, J = 8.0 Hz). MS (API-ES+): 573 (M+H).

EXAMPLE AAA17

1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-bromo-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA16, STEP C**) and 2, 4-difluorobenzene boronic acid as described in **EXAMPLE AAA16, STEP D**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.03 (s, 3H), 1.08 (s, 3H), 1.59 (brs, 2H), 2.40 (m, 2H), 2.56 (brs, 1H), 2.83 (m, 1H), 2.90 (brs, 1H), 3.15 (s, 1H), 3.58 (abq, 3H, J = 14.5 Hz), 3.81 (s, 3H), 4.20 (brs, 2H), 4.58 (brs, 2H), 6.23 (s, 1H), 6.85 (m, 3H), 6.91 (m, 2H), 7.14 (q, 1H, J = 7.1 Hz), 7.23 (d, 2H, J = 8.5 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.54 (d, 2H, J = 8.1 Hz). MS (API-ES+): 677 (M+H).

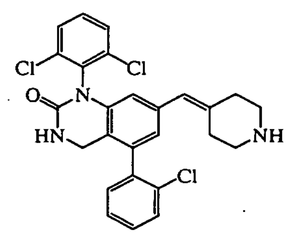
STEP B: 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one

The 1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-5-(2,4-difluorophenyl)-7-(N-isopropylbicyclo[2.2.1]piperazinylmethyl)-3,4-dihydro-2(1H)-quinazolinone as

described in **EXAMPLE AAA16, STEP E**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.03 (d, 3H, J = 5.5 Hz), 1.08 (d, 3H, J = 5.8 Hz), 1.66 (m, 2H), 2.37 (d, 1H, J = 9.2 Hz), 2.43 (d, 1H, J = 9.1 Hz), 2.56 (brs, 1H), 2.83 (d, 1H, J = 9.2 Hz), 2.91 (brs, 1H), 3.15 (s, 1H), 3.60 (abq, 3H, J = 14.2 Hz), 4.31 (brs, 1H), 4.50 (brs, 1H), 5.10 (s, 1H), 6.26 (s, 1H), 6.91 (s, 1H), 6.94 (dt, 1H, J_1 = 9.4 Hz, J_2 = 2.3 Hz), 6.99 (dt, 1H, J_1 = 8.0 Hz, J_2 = 2.3 Hz), 7.31 (m, 1H), 7.39 (d, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 8.0 Hz). MS (API-ES+): 557 (M+H).

EXAMPLE AAA18

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylidenemethyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 7-(bromomethyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one

A solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(hydroxymethyl)-3,4-dihydroquinazolin-2(1*H*)-one (500mg, 1.15mmol), triphenyl phosphine (363mg, 1.38mmol) and carbon tetrabromide (459mg, 1.38mmol) in acetonitrile (34mL) was stirred at rt for 24h. Removal of the solvent and subsequent purification by flash chromatography using 22% acetone/hexane as eluent provided 7-(bromomethyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.26 (d, 1H, J = 14.7 Hz), 4.35 (abq, 2H, J = 10.5 Hz), 4.44 (d, 1H, J = 14.6 Hz), 5.01 (s, 1H), 6.18 (s, 1H), 6.96 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 497 (M+H).

STEP B: diethyl [5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylphosphonate

A mixture of 7-(bromomethyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (55mg, 0.11mmol) and triethylphosphite (0.8mL, 4.66mmol) in DMF (0.5mL) was stirred at 100°C for 1.75h. After it was cooled to rt, the resulting mixture was treated with ether and hexane to form a precipitate. Filtration of the precipitate provided diethyl [5-(2-chlorophenyl)-

1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylphosphonate as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (m, 6H), 3.01 (s, 1H), 3.06 (s, 1H), 3.97 (m, 4H), 4.34 (abq, 2H, J = 14.1 Hz), 5.12 (s, 1H), 6.12 (s, 1H), 6.86 (s, 1H), 7.26-7.60 (m, 7H). MS (API-ES+): 553 (M+H).

STEP C: tert-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate

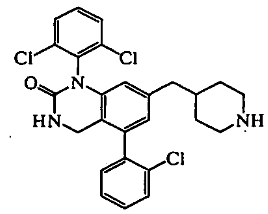
To a solution of diethyl [5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylphosphonate (422mg, 0.762mmol) in a mixture of THF (9mL) and DMF (2mL) at 0°C was added sodium hydride (60%, 61mg, 1.52mmol). The resulting mixture was stirred at rt for 20min and then cooled to 0°C again. To this was added a solution of *t*-butyl-4-oxo-1-piperidinecarboxylate (310mg, 1.524mmol) in THF (2mL). Then the reaction was stirred at rt for 22h. The mixture was quenched with brine, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and subsequent purification by flash chromatography using 20% acetone/hexane as eluent provided *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (s, 9H), 2.24 (brs, 2H), 2.31 (t, 2H, J = 5.7 Hz), 3.31 (t, 2H, J = 5.5 Hz), 3.45 (t, 2H, J = 5.5 Hz), 4.35 (abq, 2H, J = 14.4 Hz), 5.10 (s, 1H), 5.96 (s, 1H), 6.21 (s, 1H), 6.74 (s, 1H), 7.30-7.58 (m, 7H). MS (API-ES+): 600 (M+H).

STEP D: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylidenemethyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylidenemethyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate as described in **EXAMPLE AAA1, STEP B.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80 (brs, 1H), 2.26 (t, 2H, J = 5.5 Hz), 2.33 (t, 2H, J = 5.5 Hz), 2.77 (t, 2H, J = 5.5 Hz), 2.92 (t, 2H, J = 5.5 Hz), 4.35 (abq, 2H, J = 14.4 Hz), 5.12 (s, 1H), 5.96 (s, 1H), 6.15 (s, 1H), 6.74 (s, 1H), 7.30-7.56 (m, 7H). MS (API-ES+): 500 (M+H).

EXAMPLE AAA19

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: tert-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate

A solution of *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate (**EXAMPLE AAA18, STEP C**, 150mg, 0.25mmol) in ethyl acetate (4mL) was purged and filled with nitrogen. To this was added platinum (IV) oxide hydrate (30mg, 20 % weight). The mixture was evacuated and filled with hydrogen via balloon. Then the reaction was stirred at rt under hydrogen for 1h, filtered through celite and rinsed with ethyl acetate and methanol. Removal of the solvent provided *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate as a white solid used directly for the next step.

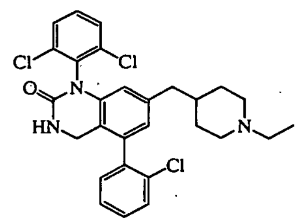
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (m, 2H), 1.46 (s, 9H), 1.55 (m, 3H), 2.40 (m, 2H), 2.61 (t, 2H, J = 12.4 Hz), 4.04 (d, 2H, J = 12.8 Hz), 4.33 (abq, 2H, J = 14.2 Hz), 5.19 (s, 1H), 5.91 (s, 1H), 6.70 (s, 1H), 7.28-7.60 (m, 7H).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate as described in **EXAMPLE AAA1, STEP B**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17 (m, 2H), 1.54 (m, 1H), 1.63 (d, 2H, J = 12.3 Hz), 2.40 (m, 2H), 2.57 (m, 2H), 2.80 (brs, 1H), 3.11 (d, 2H, J = 12.4 Hz), 4.35 (abq, 2H, J = 14.4 Hz), 5.27 (s, 1H), 5.90 (s, 1H), 6.69 (s, 1H), 7.29-7.56 (m, 7H). MS (API-ES+): 500 (M+H).

EXAMPLE AAA20

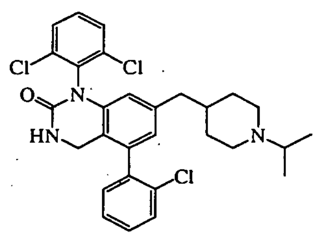
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-ethylpiperidin-4-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared as a byproduct from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA19**) and cyclopropyl methyl ketone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.08 (t, 3H, J = 7.1 Hz), 1.24 (m, 2H), 1.40 (m, 1H), 1.61 (brs, 2H), 1.80 (t, 2H, J = 10.5 Hz), 2.80 (brs, 1H), 2.39 (m, 4H), 2.90 (d, 2H, J = 11.0 Hz), 4.33 (abq, 2H, J = 14.2 Hz), 5.01 (s, 1H), 5.91 (s, 1H), 6.70 (s, 1H), 7.29-7.58 (m, 7H). MS (API-ES+): 530 (M+H).

EXAMPLE AAA21

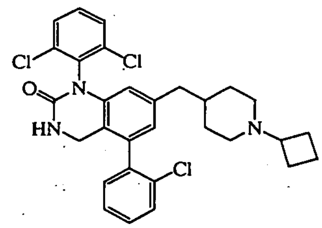
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-isopropylpiperidin-4-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA19**) and acetone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.04 (brs, 6H), 1.20 (brs, 1H), 1.38 (brs, 1H), 1.61 (brs, 3H), 2.04 (brs, 2H), 2.40 (d, 2H, J = 6.2 Hz), 2.68 (brs, 1H), 2.84 (brs, 2H), 4.33 (d of abq, 2H, J_1 = 14.2 Hz, J_2 = 1.6 Hz), 5.05 (s, 1H), 5.32 (s, 1H), 5.90 (s, 1H), 6.69 (s, 1H), 7.29-7.56 (m, 7H). MS (API-ES+): 542 (M+H).

EXAMPLE AAA22

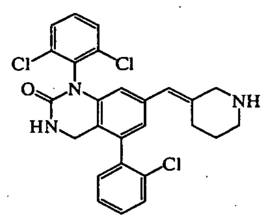
5-(2-chlorophenyl)-7-[(1-cyclobutylpiperidin-4-yl)methyl]-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA19**) and cyclobutanone as described in **EXAMPLE AAA1, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (m, 2H), 1.38 (brs, 1H), 1.66 (m, 6H), 1.86 (t, 2H, J = 8.4 Hz), 2.02 (m, 2H), 2.40 (d, 2H, J = 5.7 Hz), 2.63 (m, 1H), 2.82 (d, 2H, J = 9.1 Hz), 4.33 (abq, 2H, J = 14.2 Hz), 5.01 (s, 1H), 5.90 (s, 1H), 6.69 (s, 1H), 7.29-7.56 (m, 7H). MS (API-ES+): 554 (M+H).

EXAMPLE AAA23

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(*E*)-piperidin-3-ylidenemethyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: *tert*-butyl (3*E*)-3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate

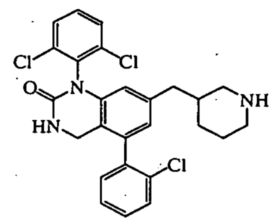
The *tert*-butyl (3*E*)-3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate was prepared from diethyl [5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylphosphonate (**EXAMPLE AAA18, STEP B**) as described in **EXAMPLE AAA18, STEP C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (s, 9H), 1.52 (m, 2H), 1.67 (m, 1H), 2.37 (m, 2H), 3.45 (m, 2H), 3.92 (s, 1H), 4.35 (abq, 2H, J = 14.4 Hz), 5.04 (s, 1H), 5.99 (s, 1H), 6.26 (s, 1H), 6.76 (s, 1H), 7.30-7.58 (m, 7H). MS (API-ES+): 600 (M+H).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(*E*)-piperidin-3-ylidenemethyl]-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(*E*)-piperidin-3-ylidenemethyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from *tert*-butyl (3*E*)-3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate as described in **EXAMPLE AAA1, STEP B.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.60 (m, 3H), 2.40 (t, 2H, J = 5.7 Hz), 3.01 (s, 2H), 3.45 (s, 2H), 4.35 (abq, 2H, J = 14.0 Hz), 5.04 (s, 1H), 5.99 (s, 1H), 6.25 (s, 1H), 6.75 (s, 1H), 7.30-7.60 (m, 7H). MS (API-ES+): 500 (M+H).

EXAMPLE AAA24

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: *tert*-butyl 3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate

The *tert*-butyl 3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate was prepared from *tert*-butyl (3*E*)-3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methylene}piperidine-1-carboxylate (**EXAMPLE AAA23, STEP A**) as described in **EXAMPLE AAA19, STEP A**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (brs, 1H), 1.40 (s, 9H), 1.60 (m, 3H), 1.70 (m, 1H), 2.30 (brs, 1H), 2.45 (brs, 2H), 2.70 (m, 1H), 3.90 (brs, 2H), 4.33 (d, 2H, J = 14.4Hz), 5.15 (s, 1H), 5.93 (s, 1H), 6.70 (s, 1H), 7.28-7.60 (m, 7H).

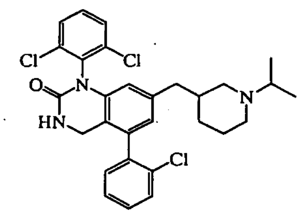
STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from *tert*-butyl 3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]methyl}piperidine-1-carboxylate as described in **EXAMPLE AAA1, STEP B.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (m, 1H), 1.46 (m, 1H), 1.66 (m, 2H), 1.74 (m, 1H), 2.26 (m, 2H), 2.37 (m, 2H), 2.54 (m, 1H), 3.03 (m, 2H), 4.33 (abq, 2H, J = 14.4 Hz),

5.20 (s, 1H), 5.90 (s, 1H), 6.69 (s, 1H), 7.25-7.60 (m, 7H). MS (API-ES+): 500 (M+H).

EXAMPLE AAA25

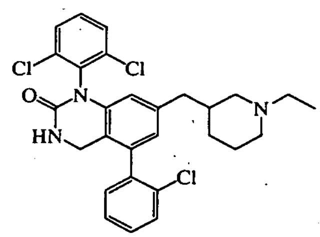
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-isopropylpiperidin-3-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA24**) and acetone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.83 (m, 1H), 0.99 (m, 6H), 1.46 (m, 1H), 1.66 (m, 4H), 2.05 (t, 1H, J = 11.4 Hz), 2.38 (m, 2H), 2.68 (m, 2H), 2.78 (m, 1H), 4.24 (d, 1H), 4.41 (dd, 1H, J_1 = 14.2 Hz, J_2 = 6.7 Hz), 5.04 (s, 1H), 5.92 (s, 1H), 6.70 (s, 1H), 7.22-7.60 (m, 7H). MS (API-ES+): 542 (M+H) n.

EXAMPLE AAA26

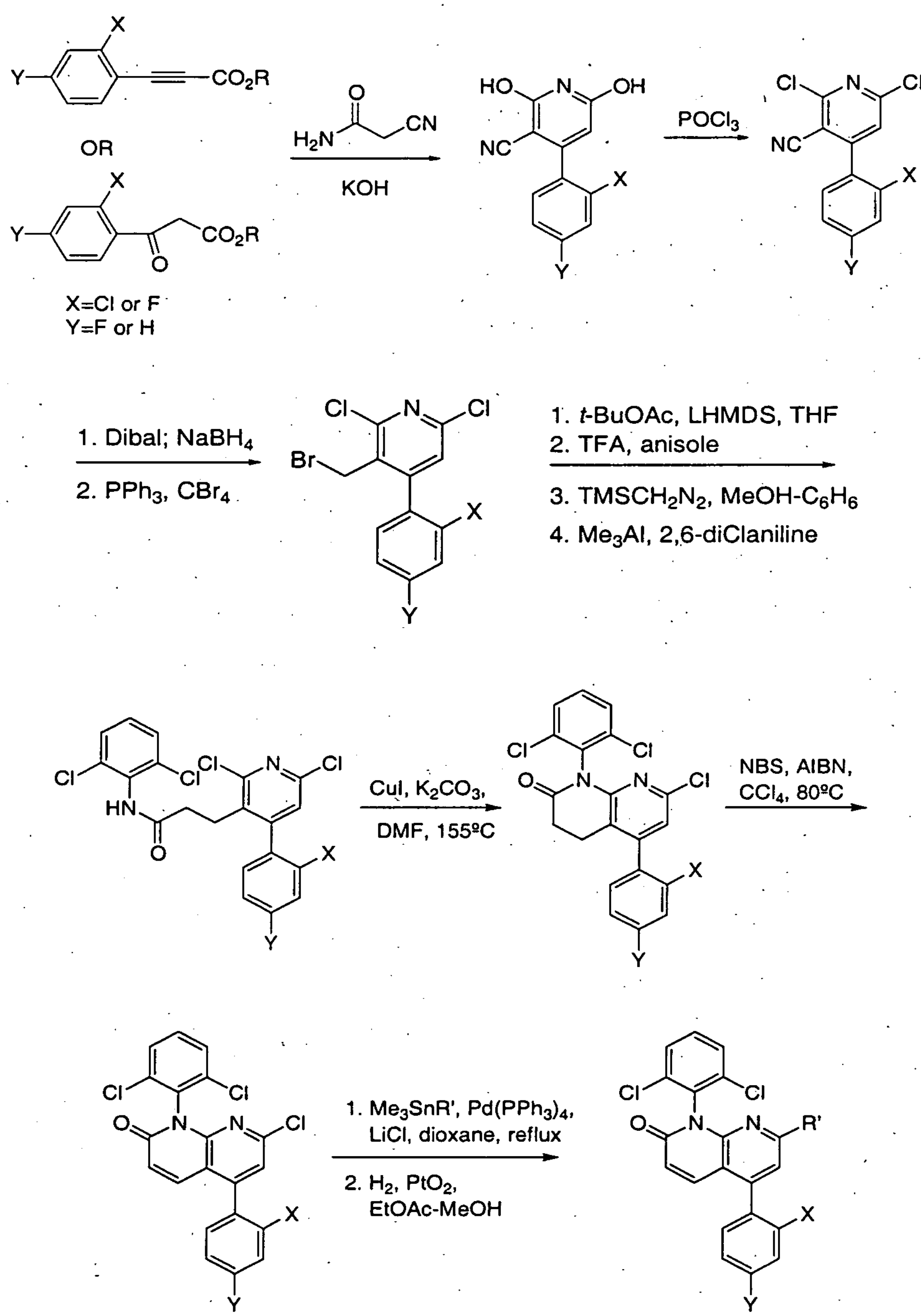
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-ethylpiperidin-3-yl)methyl]-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared as a byproduct from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE AAA24**) and cyclopropyl methyl ketone as described in **EXAMPLE AAA1, STEP A.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.85 (m, 1H), 1.04 (brs, 3H), 1.52 (m, 2H), 1.65 (m, 2H), 1.75 (m, 2H), 2.35 (m, 3H), 2.43

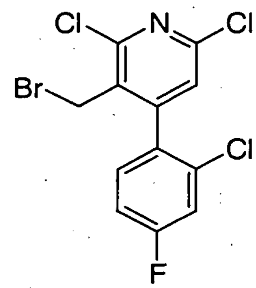
(m, 41H), 2.76 (m, 1H), 2.85 (m, 1H), 4.33 (abq, 2H, J = 14.4 Hz), 5.00 (s, 1H), 5.92 (s, 1H), 6.70 (s, 1H), 7.24-7.60 (m, 7H). MS (API-ES+): 530 (M+H).

Compounds of this invention can be made according to the scheme shown below:



COMPOUND BBB1

3-(bromomethyl)-2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridine



STEP A: 4-(2-chloro-4-fluorophenyl)-2,6-dihydroxynicotinonitrile

Potassium hydroxide (5.1g, 91mmol) was added to a solution of 2-cyanoacetamide (7.2g, 86mmol) in 270mL ethanol and stirred briefly at rt. A solution of ethyl 3-(2-chloro-4-fluorophenyl)prop-2-ynoate (3.58g, 16.9mmol) in 30mL ethanol was added and the solution stirred for 10min (heavy precipitate). The resulting suspension was then refluxed for 1h and stirred overnight at rt. The mixture was concentrated and the solid residue (4-(2-chloro-4-fluorophenyl)-2,6-dihydroxynicotinonitrile) was used without further purification. Mass spectrum (ESI) 265 (M+1).

(Ethyl 3-(2-chloro-4-fluorophenyl)prop-2-ynoate was prepared from 2-chloro-4-fluorobenzaldehyde as described by Chenault, J.; Dupin, J. E. *Synthesis* **1987**, *5*, 498.)

STEP B: 2,6-dichloro-4-(2-chloro-4-fluorophenyl)nicotinonitrile

Crude 4-(2-chloro-4-fluorophenyl)-2,6-dihydroxynicotinonitrile (16.9mmol theoretical) was heated in 50mL phosphorous oxychloride at 175°C in a sealed tube. After 15h the solution was cooled and concentrated. Water was added to the residue and the resultant mixture extracted with ethyl acetate (3X). The combined extracts were washed with water, brine and dried over magnesium sulfate. The solvent was concentrated and the residue crystallized from ethyl ether/hexanes to give 2,6-dichloro-4-(2-chloro-4-fluorophenyl)nicotinonitrile as a light brown solid. More product was obtained after silica gel chromatography purification (1/9 ethyl acetate/hexanes eluent) of the supernatant. Mass spectrum (ESI) 301 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18-7.22(m, 1H); 7.34-7.39(m, 2H); 7.41(s, 1H).

STEP C: [2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridin-3-yl]methanol

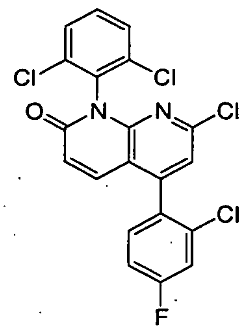
Diisobutylaluminum hydride (1.5M toluene, 1.56mL, 2.34mmol) was added dropwise to a solution of 2,6-dichloro-4-(2-chloro-4-fluorophenyl) nicotinonitrile (0.644g, 2.14mmol) in dichloromethane at 0°C. The solution was stirred at 0°C until no starting material remained (TLC analysis, 1h). The solution was concentrated and 50mL THF/2N HCl (9/1) was added to the residue. After stirring 15min the solution was concentrated and the residue partitioned between water and dichloromethane. The phases were separated and the organic concentrated. The residue was dissolved in 50mL THF/pH 7 buffer (9/1) and cooled to 0°C. Sodium borohydride (200mg, 5.4mmol) was added and the solution stirred for 40min. The solution was then concentrated and the residue partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue ([2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridin-3-yl]methanol) was used without further purification. Mass spectrum (ESI) 306 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37(d, 1H, J=12.6Hz); 4.69(d, 1H, J=12.6Hz); 7.12-7.17(m, 1H); 7.20(s, 1H); 7.28-7.35(m, 2H).

STEP D: 3-(bromomethyl)-2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridine.

Triphenyl phosphine (0.67g, 2.55mol) and carbon tetrabromide (0.85g, 2.56mmol) were added to a solution of [2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridin-3-yl]methanol (2.14mmol theoretical) in 15mL acetonitrile at rt. After stirring overnight, the solution was concentrated and the residue partitioned between water and dichloromethane. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography using ethyl ether/hexanes as the eluent to give 3-(bromomethyl)-2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridine. Mass spectrum (ESI) 368 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.10(d, 1H, J=10.8Hz); 4.53(d, 1H, J=10.6Hz); 7.17(s, 1H); 7.15-7.21(m, 1H); 7.30-7.34(m, 1H); 7.36-7.41(m, 1H).

COMPOUND BBB2

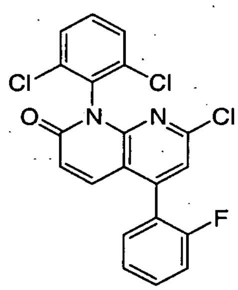
7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 3-(bromomethyl)-2,6-dichloro-4-(2-chloro-4-fluorophenyl)pyridine (**COMPOUND BBB1**) by a procedure analogous to that described in **COMPOUND HH1** and **COMPOUND HH2**. Mass spectrum (ESI) 453 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8 (d, 1H, J=9.9Hz); 7.13 (s, 1H); 7.18-7.24 (m, 1H); 7.36-7.40(m, 2H); 7.42-7.48(m, 2H); 7.54-7.58(m, 2H).

COMPOUND BBB3

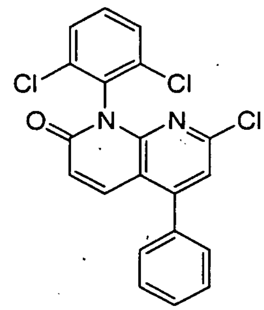
7-chloro-5-(2-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared as described in **COMPOUND BBB2** and **COMPOUND BBB1** with the following exception: 4-(2-fluorophenyl)-2,6-dihydroxynicotinonitrile was prepared from 2-cyanoacetamide and ethyl 3-(2-fluorophenyl)-3-oxopropanoate as described by Katritzky, A. R.; et al *J. Heterocycl. Chem.* **1995**, *32*, 979. Mass spectrum (ESI) 419 (M+1).

COMPOUND BBB4

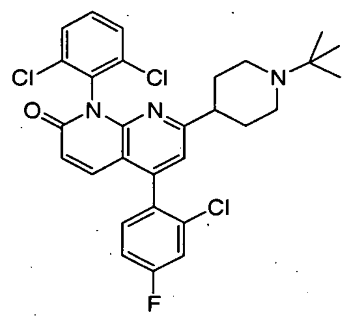
7-chloro-1-(2,6-dichlorophenyl)-5-phenyl-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared by a procedure analogous to that described in **COMPOUND BBB3**. Mass spectrum (ESI) 401 (M+1).

EXAMPLE BBB1

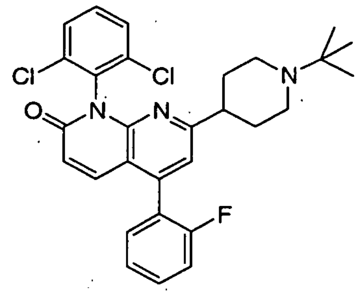
7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) by a procedure analogous to that described in **EXAMPLE HH1**. Mass spectrum (ESI) 558 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.15(s, 9H); 1.61-1.77(m, 2H); 1.89-1.96(m, 2H); 2.41-2.52(m, 2H); 2.77-2.86(m, 1H); 3.08-3.18(m, 2H); 6.75(d, 1H, J=9.6Hz); 7.29-7.34(m, 1H); 7.48-7.55(m, 3H); 7.61-7.64(m, 2H); 7.66(d, 1H, J=9.9Hz).

EXAMPLE BBB2

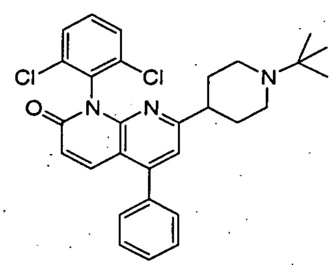
7-(1-*tert*-butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB3**) by a procedure analogous to that described in **EXAMPLE HH1**. Mass spectrum (ESI) 524 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.10(s, 9H); 1.64-1.73(m 2H); 1.83-1.90(m, 2H); 2.29-2.38(m, 2H); 2.70-2.79(m, 1H); 3.01-3.09(m, 2H); 6.75(d, 1H, 9.9Hz); 7.24(s, 1H); 7.32-7.43(m, 2H); 7.46-7.54(m, 2H); 7.57-7.63(m, 3H); 7.77-7.82(m, 1H).

EXAMPLE BBB3

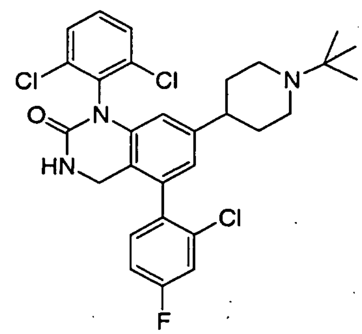
7-(1-*tert*-butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-phenyl-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-1-(2,6-dichlorophenyl)-5-phenyl-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB4**) by a procedure analogous to that described in **EXAMPLE HH1**. Mass spectrum (ESI) 506 (M+1).). ^{1}H NMR (500 MHz, CD_3OD): δ 1.09(s, 9H); 1.62-1.72(m, 2H); 1.82-1.89(m, 2H); 2.25-2.33(m, 2H); 2.68-2.76(m, 1H); 3.00-3.07(m, 2H); 6.74(d, 1H, J=9.8Hz); 7.22(s, 1H); 7.49-7.63(m, 8H); 8.03(d, 1H, J=9.8Hz).

EXAMPLE BBB4

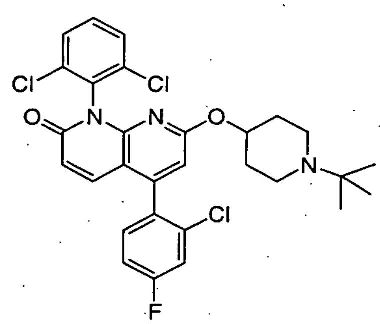
7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 1-(2,6-dichlorophenyl)-5-(2-chloro-4-fluorophenyl)-7-oxytrifluormethylsulfunyl-3,4-dihydro-2(1H)-quinazolinone (**INTERMEDIATE 62**) by a procedure analogous to that described in **EXAMPLE HH1**. Mass spectrum (ESI) 560 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.10(s, 9H); 1.50-1.60(m, 2H); 1.74-1.79(m, 2H); 2.21-2.30(m, 2H); 2.37-2.45(m, 1H); 3.09-3.15(m, 2H); 4.24(m, 2H); 6.03(s, 1H); 6.78(s, 1H); 7.17-7.22(m, 1H); 7.34-7.39(m, 2H); 7.51(t, 1H, J=8.1Hz); 7.60-7.64(m, 2H).

EXAMPLE BBB5

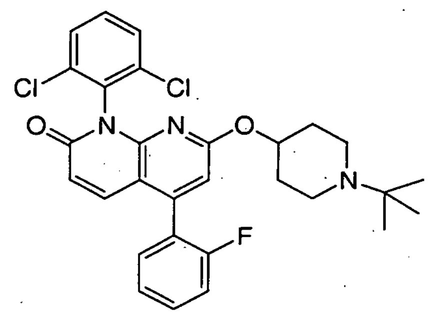
7-[(1-*tert*-butylpiperidin-4-yl)oxy]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) by a procedure analogous to that described in **EXAMPLE HH10**. Mass spectrum (ESI) 574 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.12(s, 9H); 1.60-1.71(m, 2H); 1.82-1.91(m, 2H); 2.13-2.26(m, 2H); 2.88-2.96(m, 2H); 4.34-4.42(m, 1H); 6.61(s, 1H); 6.63(d, 1H, J=3.4Hz); 7.27-7.30(m, 1H); 7.47-7.50(m, 2H); 7.54-7.58(m, 2H); 7.65-7.69(m, 2H).

EXAMPLE BBB6

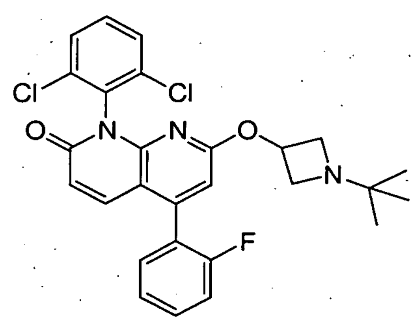
7-[(1-tert-butylpiperidin-4-yl)oxy]-1-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-1,8-naphthyridin-2(1H)-one



The title compound was prepared from 7-chloro-5-(2-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB3**) by a procedure analogous to that described in **EXAMPLE HHH10**. Mass spectrum (ESI) 540 (M+1).

EXAMPLE BBB7

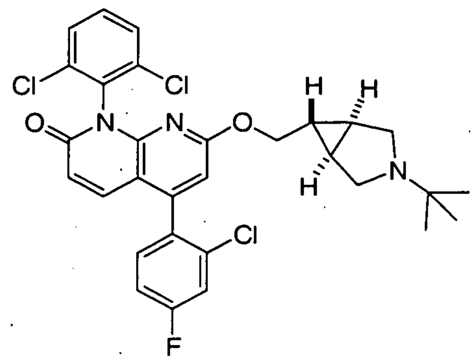
7-[(1-*tert*-butylazetidin-3-yl)oxy]-1-(2,6-dichlorophenyl)-5-(2-fluorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB3**) by a procedure analogous to that described in **EXAMPLE RRR-4**. Mass spectrum (ESI) 512 (M+1). (1-*tert*-Butylazetidin-3-ol was prepared as described by Gaertner, V. *Tetrahedron Letters* **1966**, 4691.)

EXAMPLE BBB8

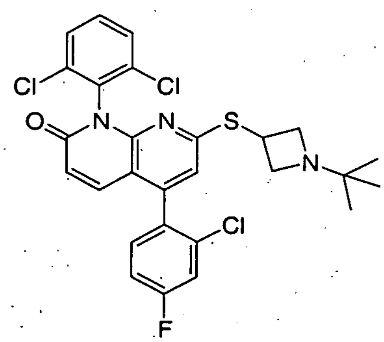
7-{[(1*R*,5*S*)-3-*tert*-butyl-3-azabicyclo[3.1.0]hex-6-yl]methoxy}-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) by a procedure analogous to that described in **EXAMPLE HHH10**. Mass spectrum (ESI) 586 (M+1). (The requisite primary alcohol was prepared by a procedure analogous to that described in Brighty, K. E.; Castaldi, M. J. *SYNLETT* **1996**, 1097.)

EXAMPLE BBB9

7-[(1-*tert*-butylazetidin-3-yl)thio]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one

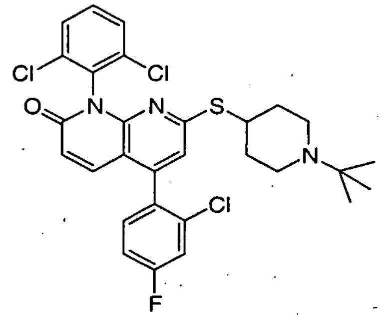


Potassium thioacetate (69mg, 0.60mmol) was added to a solution of 1-*tert*-butylazetidin-3-yl 4-methylbenzenesulfonate (103mg, 0.36mmol) in 1.5mL dimethylformamide. After stirring at 50°C overnight, the solution was cooled to rt and sodium borohydride (30mg, 0.8mmol) was added. After stirring for 1 hour, 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) (30mg, 0.07mmol) was added. The solution was then stirred at 50°C for 1.5h. The reaction mixture was concentrated and the crude residue partitioned between ethyl acetate and K_2CO_3 aq. The organic phase was dried over

magnesium sulfate and concentrated. The residue was purified by preparative thin layer silica gel chromatography using EtOAc/MeOH/Et_3N (98.5/1/0.5) as the eluent to give the title compound. Mass spectrum (ESI) 562 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 0.93(s, 9H); 3.01-3.07(m, 2H); 3.15-3.20(m, 2H); 3.67-3.74(m, 1H); 6.69(d, 1H, J=9.8Hz); 7.12(s, 1H); 7.28-7.33(m, 1H); 7.47-7.51(m, 2H); 7.57-7.63(m, 2H); 7.69-7.73(m, 2H). (1-*tert*-Butylazetidin-3-yl 4-methylbenzenesulfonate was prepared as described by Okutani, T.; et al *Chem. Pharm. Bull.* **1974**, *22*, 1490.)

EXAMPLE BBB10

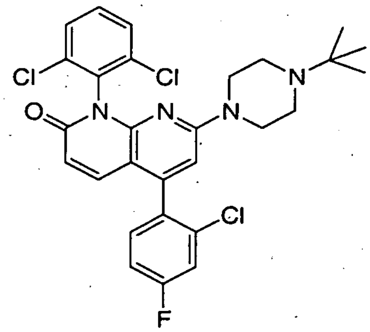
7-[(1-*tert*-butylpiperidin-4-yl)thio]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) by a procedure analogous to that described in **EXAMPLE BBB9**. Mass spectrum (ESI) 590 (M+1).

EXAMPLE BBB11

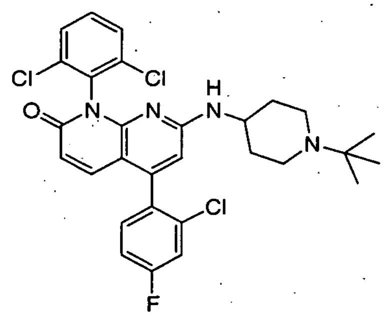
7-(4-*tert*-butylpiperazin-1-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) and 1-*tert*-butylpiperazine by a procedure analogous to that described in **EXAMPLE CCC6**. Mass spectrum (ESI) 559 (M+1). (1-*tert*-Butylpiperazine was prepared as described by Cook, M. J.; et al *J.C.S. Perkin II* **1973**, 325.)

EXAMPLE BBB12

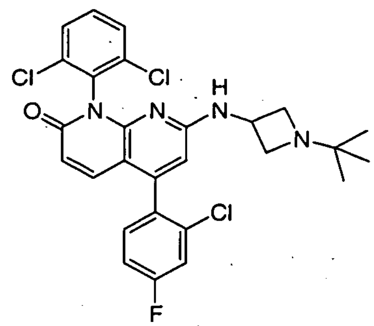
7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) and 1-*tert*-butylpiperidin-4-amine (**COMPOUND BBB5**) by a procedure analogous to that described in **EXAMPLE CCC6**. Mass spectrum (ESI) 573 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08(s, 9H); 1.27-1.42(m, 2H); 1.80-2.00(m, 4H); 2.85-2.95(m, 2H); 3.18-3.28(m, 1H); 4.67(m, 1H); 6.13(s, 1H); 6.45(d, 1H, J=9.6Hz); 7.12-7.17(m, 1H); 7.26-7.38(m, 4H); 7.49-7.54(m, 2H).

EXAMPLE BBB13

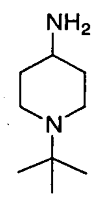
7-[(1-*tert*-butylazetidin-3-yl)amino]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) and 1-*tert*-butylazetidin-3-amine by a procedure analogous to that described in **EXAMPLE CCC6**. Mass spectrum (ESI) 545 (M+1). (1-*tert*-Butylazetidin-3-amine was prepared as described by Okutani, T.; et al *Chem. Pharm. Bull.* **1974**, *22*, 1490)

COMPOUND BBB5

1-*tert*-butylpiperidin-4-amine



STEP A: N-benzyl-1-*tert*-butylpiperidin-4-amine

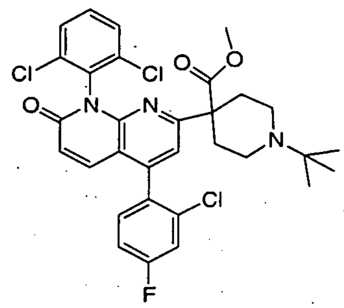
A dichloromethane solution (3mL) containing 1-*tert*-butylpiperidin-4-one (**COMPOUND PPA-1**) (120mg, 0.77mmol), benzyl amine (0.17mL, 1.56mmol), acetic acid (0.05mL) and sodium triacetoxy borohydride (246mg, 1.16mmol) was stirred for several days. The solution was concentrated and the residue partitioned between aqueous potassium carbonate and ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography using $CHCl_3/MeOH/NH_4OH$ (87/12/1) as eluent to give *N*-benzyl-1-*tert*-butylpiperidin-4-amine. Mass spectrum (ESI) 247 (M+1). ^1H NMR (500 MHz, CD_3OD): δ 1.09(s, 9H); 1.38-1.48(m, 2H); 1.91-1.97(m, 2H); 2.11-2.18(m, 2H); 2.40-2.48(m, 1H); 3.02-3.08(m, 2H); 3.76(s, 2H); 4.87(s, 1H); 7.21-7.26(m, 1H); 7.29-7.36(m, 4H).

STEP B: 1-*tert*-butylpiperidin-4-amine

A solution of *N*-benzyl-1-*tert*-butylpiperidin-4-amine (150mg) and 10% palladium on carbon (200mg) in 30mL of MeOH was hydrogenated in a Parr shaker at 50psi for 16h. The solution was filtered and concentrated to give 1-*tert*-butylpiperidin-4-amine which was used without further purification. Mass spectrum (ESI) 157 (M+1).

EXAMPLE BBB14

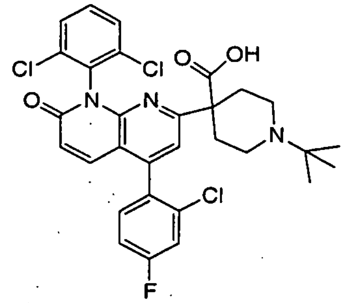
methyl 1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxylate



A solution of LHMDS (1.0M in THF, 0.2mL) was added to methyl 1-*tert*-butylpiperidine-4-carboxylate (31mg, 0.16mmol) in 2mL THF at –78°C. After 20minutes the solution was warmed to 0°C and stirred for an additional 10minutes. 7-Chloro-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (**COMPOUND BBB2**) (28.5mg, 0.063mmol) was added and the reaction mixture stirred at 45°C for 30min. The solution was cooled to rt and quenched with saturated NH_4Cl. The mixture was then partitioned between water and ethyl acetate. The organic phase was washed with water, brine and dried over magnesium sulfate. The filtered solution was concentrated and the residue purified by preparative silica gel thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (87/12/1) as eluent to give the title compound. Mass spectrum (ESI) 616 (M+1). (Methyl 1-*tert*-butylpiperidine-4-carboxylate was prepared from 1-*tert*-butylpiperidin-4-one (**COMPOUND PPA-1**) by a procedure analogous to that described by Street, L. J.; et al *J. Med. Chem.* **1990**, *33*, 2690.)

EXAMPLE BBB15

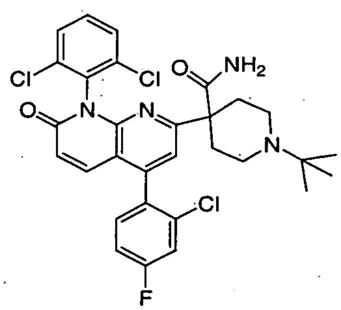
1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxylic acid



A solution of LiOH hydrate (15mg) in 0.5mL water was added to methyl 1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxylate (**EXAMPLE BBB9**) (6.4mg, 0.01mmol) in 0.5mL THF. After stirring 2 days, the solution was concentrated and the residue treated with 2mL 2N HCl. The mixture was extracted with ethyl acetate(2X) and the combined organics washed with water and brine. The solvent was dried over magnesium sulfate and concentrated to give the title compound. Mass spectrum (ESI) 602 (M+1).

EXAMPLE BBB16

1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxamide

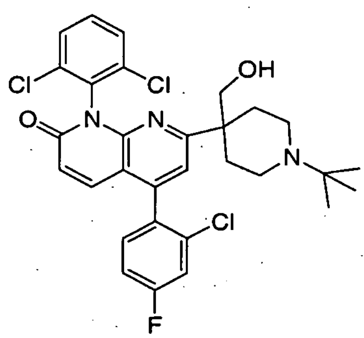


To a suspension of ammonium chloride (15.5mg, 0.29mmol) in 1mL benzene at 0°C was added trimethylaluminum(2.0M in toluene, 0.15mL). The reaction was warmed to rt and stirred for 1h. Methyl 1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxylate (**EXAMPLE BBB9**) (9.7mg, 0.016mmol) was added and the solution was stirred overnight at 50°C. The solution was then heated at 80°C for 10h. The solution was then cooled to rt and concentrated. The residue was partitioned between EtOAc/$NaHCO_3$ sat. The organic phase was washed with water, brine, dried

over magnesium sulfate and filtered. The solution was concentrated and the residue purified by preparative silica gel thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (95/5/0.5) as the eluent to give the title compound. Mass spectrum (ESI) 601 (M+1).

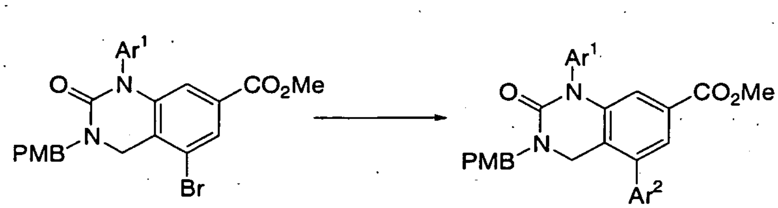
EXAMPLE BBB17

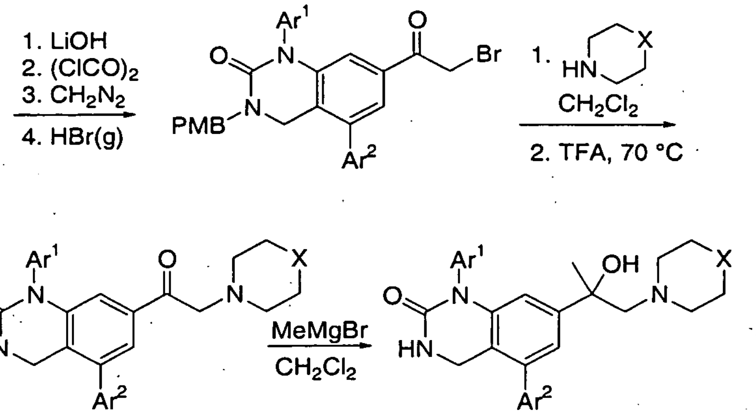
7-[1-*tert*-butyl-4-(hydroxymethyl)piperidin-4-yl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one



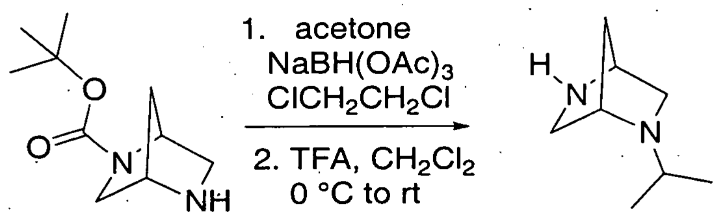
Lithium aluminum hydride (1.0M THF, 0.1mL) was added dropwise to a solution of methyl 1-*tert*-butyl-4-[4-(2-chloro-4-fluorophenyl)-8-(2,6-dichlorophenyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl]piperidine-4-carboxylate (**EXAMPLE BBB9**) (10.4mg, 0.017mmol) in 0.5mL THF at 0°C. After 20min, the reaction was quenched with 2N HCl. The reaction mixture was extracted with ethyl acetate (2X) and the combined extracts washed with water and brine. The solution was concentrated and the residue purified by preparative silica gel thin layer chromatography using $CHCl_3/MeOH/NH_4OH$ (95/5/0.5) as the eluent to give the title compound. Mass spectrum (ESI) 588 (M+1).

SCHEME ABA-1

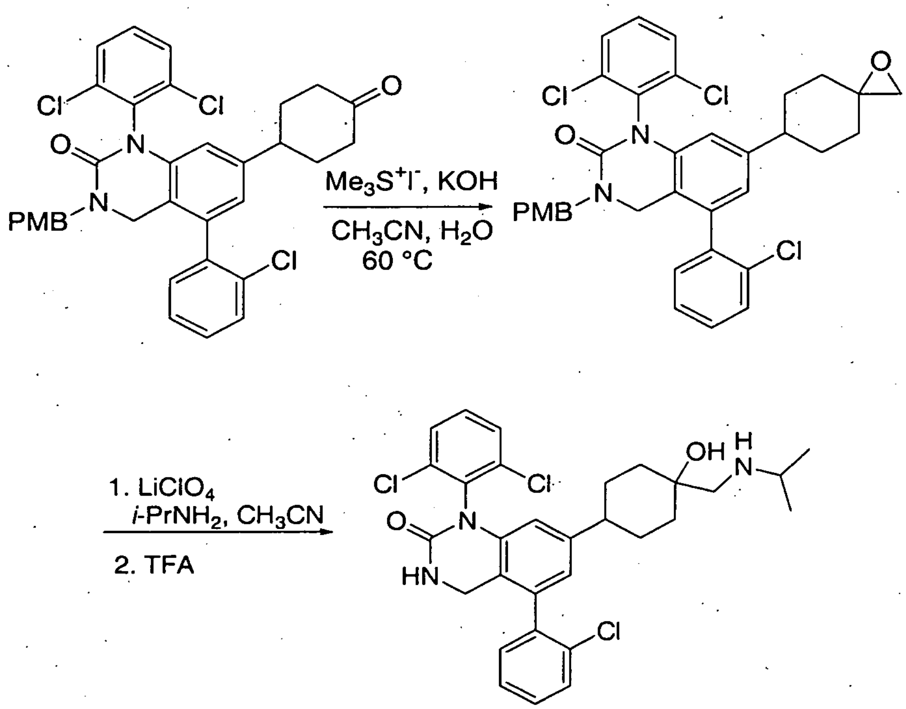




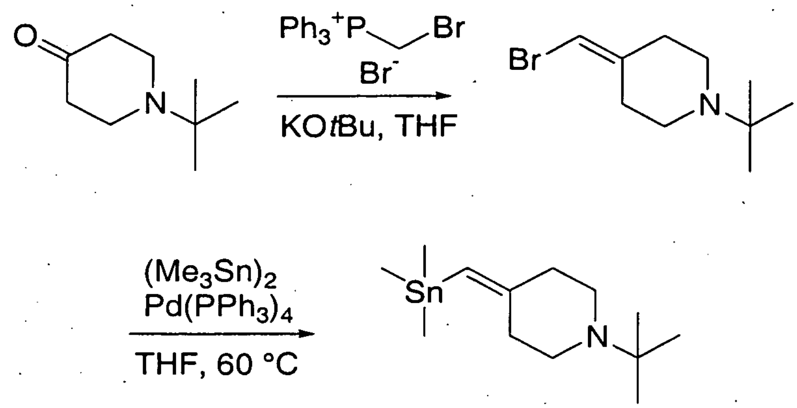
SCHEME ABA-2



SCHEME ABA-3



SCHEME ABA-4



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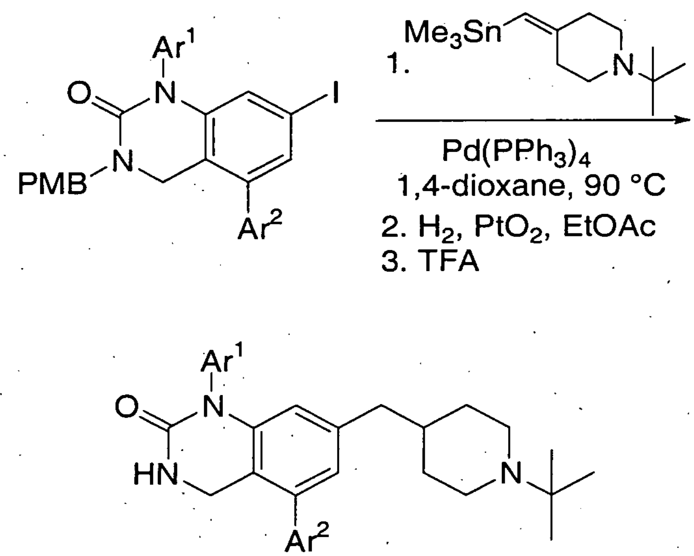
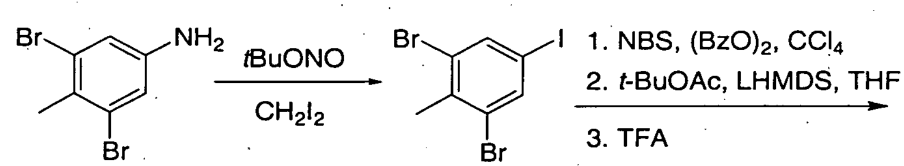
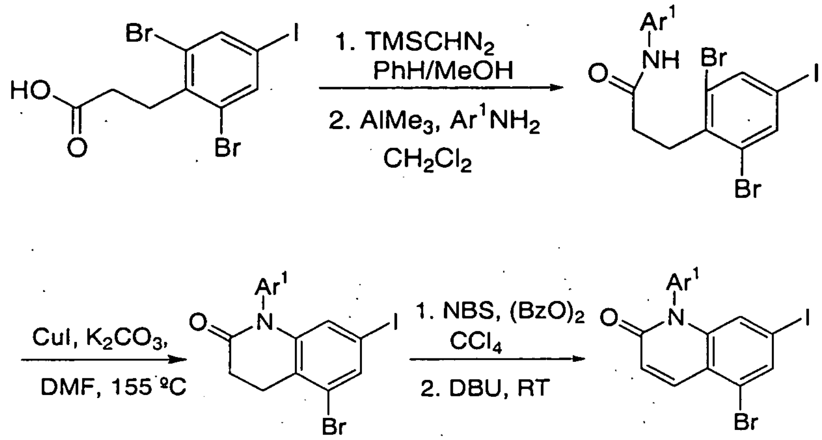
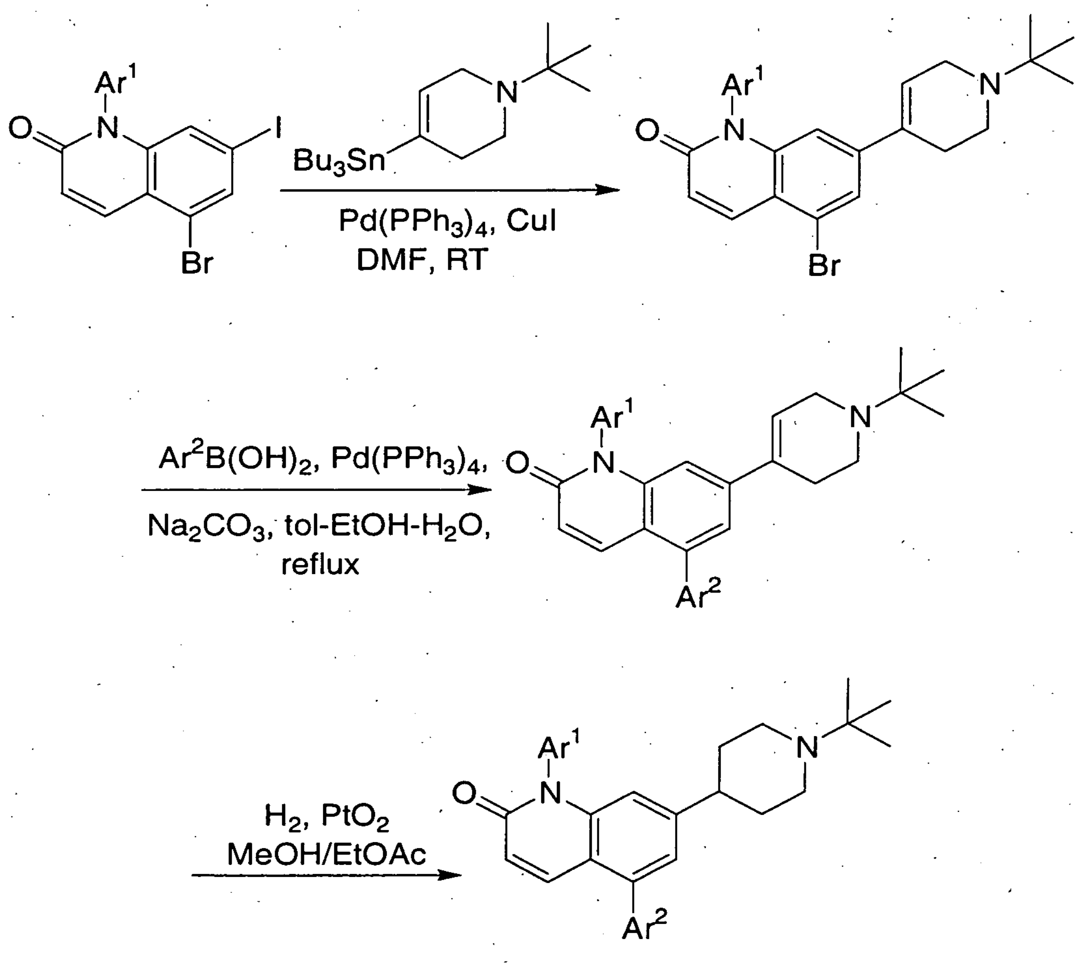


SCHEME ABA-6



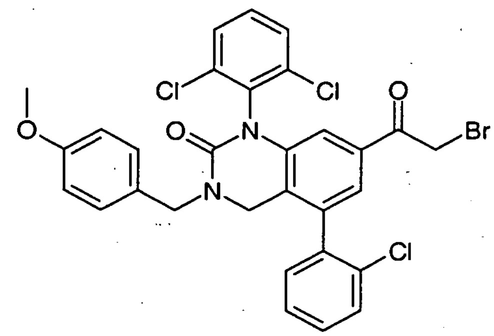


SCHEME ABA-7



INTERMEDIATE ABA1

7-(Bromoacetyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step A: Methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate

The title compound was prepared from methyl 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**INTERMEDIATE 28**) as described in **INTERMEDIATE 29**.

Mass spectrum (ESI): 581.2 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid

The title compound was prepared from methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**INTERMEDIATE ABA1, Step A**) as described **INTERMEDIATE 59**.

Mass spectrum (ESI): 567 (M+1).

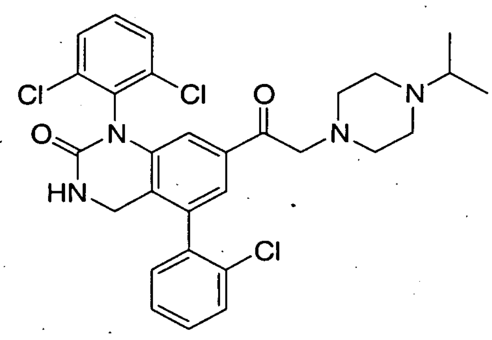
Step C: 7-(Bromoacetyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

To a solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid (770mg, 1.34mmol) in CH_2Cl_2 (10mL) at 0°C was added oxalyl chloride (175μL, 2.01mmol) followed by DMF (20μL, catalytic amount). The reaction mixture was stirred at 0°C for 10min followed by 3h at rt. After this time, the solvent was removed *in vacuo*, the residue was dissolved in THF (10mL), then the mixture was cooled down to 0°C. Diazomethane in ether was added to this slowly until the reaction mixture turned yellow and stirred for 15min at 0°C followed by 30min at rt. The excess diazomethane was quenched by addition of a few drops of acetic acid, and the solvent was removed *in vacuo* to give crude diazomethyl ketone. Diazomethyl ketone was dissolved in $CHCl_3$ (10mL) and cooled down to 0°C, and HBr was bubbled into the

reaction mixture briefly (evolution of N_2 was visible). The reaction turned dark yellow, and TLC analysis indicated the reaction was complete. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography eluting with 1:5 acetone:hexane to obtain the title compound. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.56-6.75 (m, 13 aromatic H's); 4.68 (d, J = 14.9 Hz, 1H); 4.41 (d, J = 14.9 Hz); 4.27 (m, 3H); 4.13 (d, J = 15.8 Hz, 1H); 3.8 (s, 3H).

EXAMPLE ABA1

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)acetyl]-3,4 dihydroquinazolin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)acetyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

To a solution of 7-(bromoacetyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (38mg, 0.059mmol) in CH_2Cl_2 (1 mL) was 1-isopropylpiperazine (15mg, 0.118mmol) at rt. The reaction mixture was stirred for 1.5h, then the solvent was removed *in vacuo*. The resulting crude material was purified by preparative thin layer chromatography using 10% MeOH in CH_2Cl_2 as an eluent to give the title compound. Mass spectrum (ESI): 691.2 (M+1).

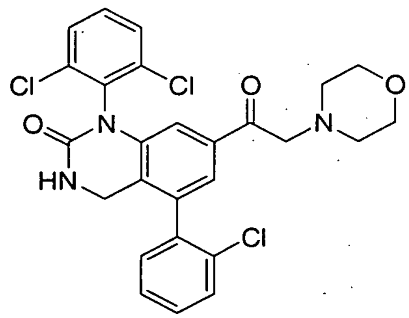
Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)acetyl]-3,4-dihydroquinazolin-2(1*H*)-one

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)acetyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (36mg, 0.052mmol) was dissolved in trifluoroacetic acid (0.8 mL), and this mixture was heated at 70°C for 30min. After cooling it down, trifluoroacetic acid was removed by co-evaporation with toluene to give crude product. This was purified by preparative thin layer chromatography using 5% 2M NH_3 in MeOH/CH_2Cl_2 as an eluent to give the title

compound. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.54-7.29 (m, 8H); 6.94 (s, 1H); 5.44 (s, 1H); 4.47 (d, J = 15.6 Hz, 1H); 4.29 (d, J = 15.6 Hz, 1H); 3.54 (Abq, J = 4.1, 14.9 Hz, 2H); 2.62 (m, 1H); 2.48 (brs, 8H); 1.03 (2 s, 6H). Mass spectrum (ESI): 571.2 (M+1).

EXAMPLE ABA2

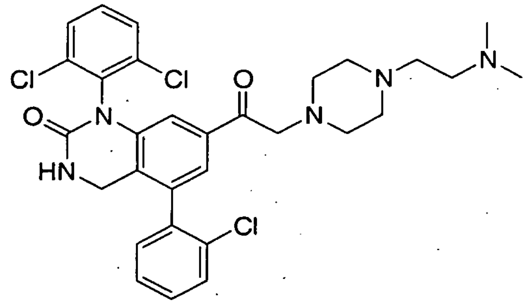
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(morpholin-4-ylacetyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 7-(bromoacetyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one and using morpholine as an amine as described in **EXAMPLE ABA1**. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.53-7.27 (m, 8H); 6.92 (s, 1H); 5.91 (brs, 1H); 4.45 (d, J = 15.5 Hz, 1H); 4.28 (d, J = 15.5 Hz, 1H); 3.64 (m, 4H); 3.55 (Abq, J = 3.7, 15.8 Hz, 2H); 2.44 (m, 4H). Mass spectrum (ESI): 530 (M+1).

EXAMPLE ABA3

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}acetyl)-3,4-dihydroquinazolin-2(1*H*)-one

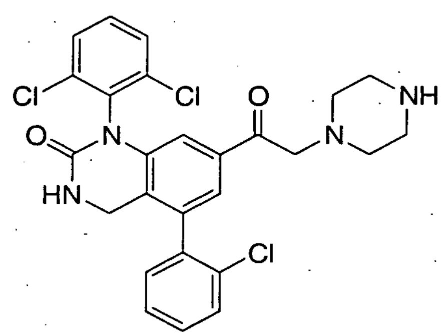


The title compound was prepared from 7-(bromoacetyl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-

2(1*H*)-one and using *N*,*N*-dimethyl-*N*-(2-piperazin-1-ylethyl)amine as an amine as described in **EXAMPLE ABA1.** ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.53-7.28 (m, 8H); 6.92 (s, 1H); 5.6 (s, 1H); 4.46 (d, J = 15.4 Hz, 1H); 4.28 (d, J = 15.4 Hz, 1H); 3.54 (Abq, J = 2.7, 16.1 Hz, 2H); 2.42 (m, 12H); 2.24 (s, 6H). Mass spectrum (ESI): 600.2 (M+1).

EXAMPLE ABA4

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperazin-1-ylacetyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step A: 2,6-Dibromo-4-iodotoluene

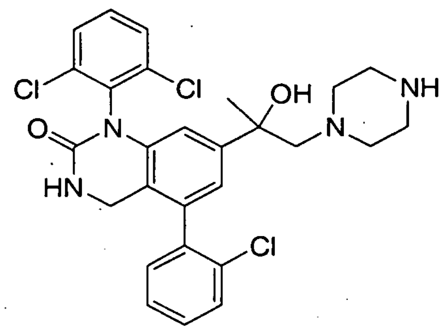
To a solution of 3,5-dibromo-4-methylaniline (4.17g, 15.74mmol) in CH_2I_2 (10mL) was added *tert*-butylnitrite (3.0mL, 23.61mmol) slowly at 0°C while stirring vigorously. The ice bath was removed and the reaction mixture was stirred at rt while the reaction was very exothermic, then placed in 80°C oil bath and heated for 20min. CH_2I_2 was distilled off under high vacuum, and the remaining residue was purified by flash chromatography eluting with 100% hexane to give the title compound.

Step B: 5-Bromo-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one

The title compound was prepared from 2.6-dibromo-4-iodotoluene by procedures analogous to that described in **COMPOUND HHH1** and **COMPOUND HHH2.** ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.2 (d, J = 9.9 Hz, 1H); 7.84 (s, 1H); 7.59-7.45 (m, 3H); 6.87 (d, J = 9.9 Hz, 1H); 6.76 (s, 1H). Mass spectrum (ESI): 496.2 (M+1).

EXAMPLE ABA5

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-hydroxy-1-methyl-2-piperazin-1-ylethyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step A: tert-Butyl 4-{2-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-2-hydroxypropyl}piperazine-1-carboxylate

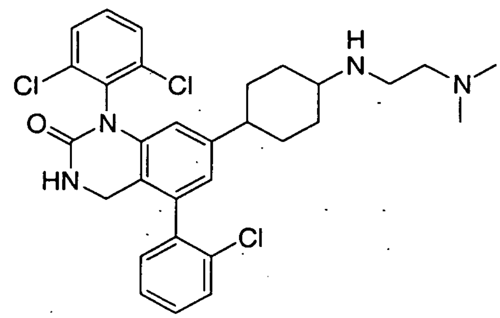
To a solution of methylmagnesium bromide (68μL, 1.4M) in CH_2Cl_2 (0.2mL) at 0°C was added *tert*-butyl 4-{2-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-2-oxoethyl}piperazine-1-carboxylate (**EXAMPLE ABA4, Step A**) (35.6mg, 0.047mmol) dissolved in CH_2Cl_2 (0.3mL) slowly. The reaction mixture was stirred for 2h while warming up to rt. It was quenched with saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the crude product was purified by preparative thin layer chromatography eluting with 1:3 acetone:hexane to obtain the title compound. Mass spectrum (ESI): 765.2 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-hydroxy-1-methyl-2 piperazin-1-ylethyl)-3,4-dihydroquinazolin-2(1*H*)-one

The title compound was prepared from *tert*-butyl 4-{2-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-2-hydroxypropyl}piperazine-1-carboxylate as described in **EXAMPLE ABA1, Step B**. Partial ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.53-7.26 (m, 7H); 5. 48 (brs, 1H); 4.4-4.2 (m, 2H); 2.7 (m, 4H); 2.22 (m, 4H); 1.3 (2s, 3H). Mass spectrum (ESI): 545.2 (M+1).

EXAMPLE ABA6

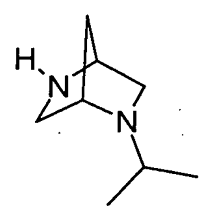
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(4-{[2-(dimethylamino)ethyl]amino}cyclohexyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(4-oxocyclohexyl)-3,4-dihydroquinazolin-2(1*H*)-one (**INTERMEDIATE 73**) and using *N,N*-dimethylethane-1,2-diamine as described in **EXAMPLE 51**. Diastereomer A ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52-7.29 (m, 7H); 6.79 (s, 1H); 5.98 (s, 1H); 5.21 (s, 1H); 4.39 (d, J = 14.2 Hz, 1H); 4.21 (d, J = 14.2 Hz, 1H); 2.77 (m, 1H); 2.61 (m, 2H); 2.38 (m, 3H); 2.19 (s, 6H); 1.74-1.51 (m, 8H). Diastereomer B ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53-7.27 (m, 7H); 6.74 (s, 1H); 5.95 (s, 1H); 5.27 (s, 1H); 4.37 (d, J = 14.4 Hz, 1H); 4.21 (d, J = 14.4 Hz, 1H); 2.68 (t, J = 6.2 Hz, 2H); 2.39 (t, J = 6.2 Hz, 2H); 2.33 (m, 2H); 2.2 (s, 6H); 1.99-1.14 (m, 8H). Mass spectrum (ESI): 571.2 (M+1).

INTERMEDIATE ABA2

2-Isopropyl-2,5-diazabicyclo[2.2.1]heptane



Step A: *tert*-Butyl 5-isopropyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The title compound was prepared from *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and using acetone as described in **EXAMPLE AAA1, Step A**.

Step B: 2-Isopropyl-2,5-diazabicyclo[2.2.1]heptane

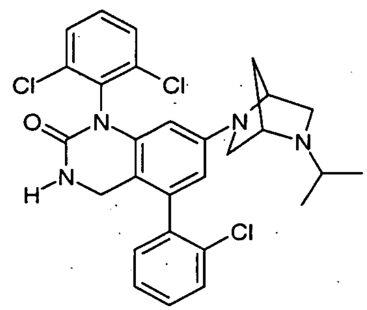
The title compound was prepared from *tert*-Butyl 5-isopropyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as described in **EXAMPLE AAA1, Step B**.

^{1}H NMR ($CDCl_3$, 500MHz): δ 3.61(s, 1H); 3.51 (s, 1H); 3.19 (d, J = 10.7 Hz, 1H); 3.15 (dd, J = 2.4, 9.7 Hz, 1H); 2.78 (d, J = 10.3 Hz, 1H); 2.62 (m, 1H);

2.27 (d, J = 9.8 Hz, 2H); 1.83 (d, J = 9.6 Hz, 1H); 1.61 (d, J = 9.8 Hz, 1H); 1.07 (d, J = 6.2 Hz, 3H); 1.04 (d, J = 6.2 Hz, 3H).

EXAMPLE ABA7

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(5-isopropyl-2,5-diazabicyclo-[2.2.1]hept-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

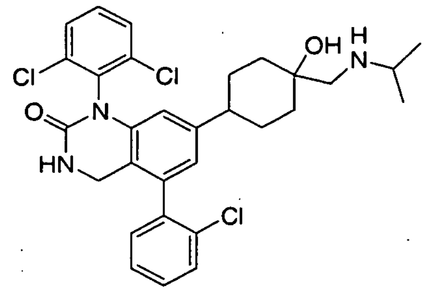
The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodo-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE CCC34**) and using 2-isopropyl-2,5-diazabicyclo[2.2.1]heptane (**INTERMEDIATE ABA2**) as described in **EXAMPLE 80**. Mass spectrum (ESI): 661.3 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(5-isopropyl-2,5-diazabicyclo-[2.2.1]hept-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE ABA7, Step A**) as described in **EXAMPLE ABA1, Step B**. ^{1}H NMR (CDCl3, 500 MHz): δ 7.52-7.31 (m, 7H); 6.07 (m, 1H); 5.3 (m, 1H); 5.13 (s, 1H); 4.32 (m, 1H); 4.13 (m, 1H); 3.88 (d, J = 31.6 Hz, 1H); 3.7 (s, 1H); 3.16-3.0 (m, 3H); 2.45 (M, 2H); 1.85 (m, 2H); 1.02 (d, J = 6.2 Hz, 6H). Mass spectrum (ESI): 541.2 (M+1).

EXAMPLE ABA8

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-hydroxy-4-[(isopropylamino)methyl]cyclohexyl}-3,4-dihydroquinazolin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-(1-oxaspiro[2.5]oct-6-yl)-3,4-dihydroquinazolin-2(1*H*)-one

To a suspension of trimethylsulfonium iodide (20mg, 0.096mmol) in CH_3CN (0.3 mL) was added one drop of H_2O followed KOH (s) (22mg, 0.384mmol). This mixture was heated at 60°C for 10min, then added 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-(4-oxocyclohexyl)-3,4-dihydroquinazolin-2(1*H*)-one (**INTERMEDIATE 76**) (40mg, 0.064mmol) in CH_3CN (0.3mL) and DMSO (0.2mL) slowly. The reaction mixture was heated another 3.5h, cooled to RT and diluted with CH_2Cl_2. It was washed with H_2O followed by brine then dried over Na_2SO_4. After removal of the solvent, the crude product was purified by preparative thin layer chromatography eluting with 1:3 acetone:hexane to give the title compound as a mixture of diastereomers. Mass spectrum (ESI): 633.2 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-hydroxy-4-[(isopropylamino)methyl]cyclohexyl}-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

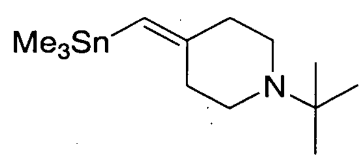
To a solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4 methoxybenzyl)-7-(1-oxaspiro[2.5]oct-6-yl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE ABA8, Step A**) (24.3mg, 0.038mmol) in CH_3CN (0.5mL) was added $LiClO_4$ (24.6mg, 0.23mmol) and isopropylamine (10.5mL, 0.114mmol). The reaction mixture was heated at 55°C for 5 days, then it was cooled. It was diluted with EtOAc, washed with H_2O and brine, then it was dried over Na_2SO_4. The crude material was purified by preparative TLC eluting with 5% 2M NH_3 in MeOH/CH_2Cl_2 to obtain diastereomer A and diastereomer B of the title compound. Mass spectrum (ESI): 692.2 (M+1).

Step C: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-hydroxy-4-[(isopropylamino)methyl]cyclohexyl}-3,4-dihydroquinazolin-2(1*H*)-one

The title compound was obtained from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-hydroxy-4-[(isopropylamino)methyl]cyclohexyl}-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (each diastereomer was reacted separately) as described in **EXAMPLE ABA1**, **Step B** as diastereomer A and diastereomer B. Diastereomer A . ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52-7.28 (m, 7H); 6.8 (s, 1H); 5.99 (s, 1H); 5.16 (s, 1H); 4.4 (d, J = 14.2 Hz, 1H); 4.22 (d, J = 14.2 Hz, 1H); 2.79 (m, 1H); 2.47 (s, 2H); 2.3 (m, 1H); 1.9-1.6 (m, 6H); 1.26 (m, 2H); 1.06 (d, J = 6.2 Hz, 6H). Diastereomer B ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53-7.28 (m, 7H); 6.74 (s, 1H); 5.96 (s, 1H); 5.2 (s, 1H); 4.39 (d, J = 14.4 Hz, 1H); 4.23 (d, J = 14.4 Hz, 1H); 2.77 (m, 1H); 2.63 (s, 2H); 2.41 (m, 1H); 1.79-1.36 (m, 8H); 1.06 (d, J = 6.4 Hz, 6H). Mass spectrum (ESI): 572.2 (M+1).

INTERMEDIATE ABA3

1-*tert*-Butyl-4-[(trimethylstannyl)methylene]piperidine



Step A: 4-(Bromomethylene)-1-*tert*-butylpiperidine

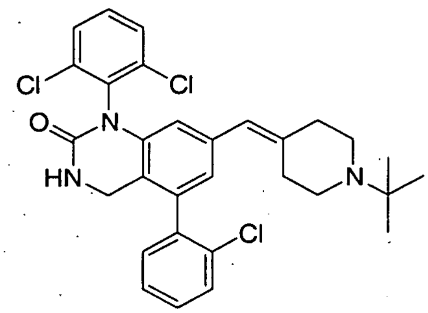
To a solution of (bromomethyl)triphenylphosphonium bromide (1.52g, 3.48mmol) in dry THF (15mL) at –78°C was added potassium *tert*-butoxide (3.5mL, 1.0M) slowly. After stirring 20 minutes, 1-*tert*-butylpiperidin-4-one (**COMPOUND PPA-1**) (595mg, 3.83mmol) in THF (2mL) was added, and the reaction mixture was warmed up to rt slowly over 2h. The reaction mixture was quenched with brine, and it was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 then concentrated *in vacuo*. The crude material was purified by flash chromatography eluting first with hexane then gradually increasing to 5% acetone/hexane to give the title compound. ^{1}H NMR ($CDCl_3$, 500MHz): δ 5.85 (s, 1H); 2.56 (m, 4H); 2.43 (t, J = 5.6 Hz, 2H); 2.28 (t, J = 5.6 Hz, 2H); 1.08 (s, 9H).

Step B: 1-*tert*-Butyl-4-[(trimethylstannyl)methylene]piperidine

The title compound was prepared from 4-(bromomethylene)-1-*tert*-butylpiperidine (**INTERMEDIATE ABA3, Step A**) as described in **INTERMEDIATE 69**. ^{1}H NMR ($CDCl_3$, 500MHz): δ 5.39 (s, 1H); 2.57 (m, 4H); 2.34 (t, J = 5.5 Hz, 2H); 2.24 (t, J = 5.5 Hz, 2H); 1.07 (s, 9H); 0.13 (s, 9H). Mass spectrum (ESI): 318.4 (M+1).

EXAMPLE ABA9

7-[(1-*tert*-Butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step A: 7-[(1-*tert*-Butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

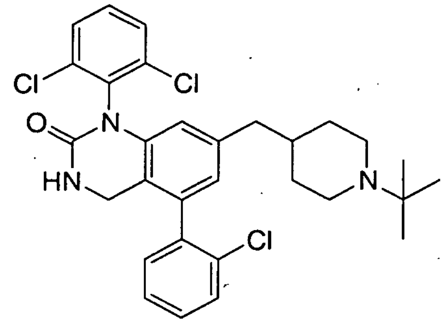
The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodo-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one **(EXAMPLE CCC34)** and using 1-*tert*-butyl-4-[(trimethylstannyl)methylene]piperidine (**INTERMEDIATE ABA3**) as described in **EXAMPLE 41, Step A**. Mass spectrum (ESI): 674.5 (M+1).

Step B: 7-[(1-*tert*-Butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one

The title compound was prepared from 7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**EXAMPLE ABA9**, **Step A**) as described in **EXAMPLE ABA1, Step B**. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.52-7.29 (m, 7H); 6.72 (s, 1H); 6.08 (s, 1H); 5.94 (s, 1H); 5.22 (, 1H); 4.41 (d, J = 14.4 Hz, 1H); 4.23 (d, J = 14.4 Hz, 1H); 2.58-2.29 (m, 8H); 1.06 (s, 9H). Mass spectrum (ESI): 554.4 (M+1).

EXAMPLE ABA10

7-[(1-*tert*-Butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



<u>**Step A**</u>: <u>7-[(1-*tert*-Butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one</u>

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodo-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (Kallashi) and using 1-*tert*-butyl-4-[(trimethylstannyl)methylene]piperidine as described in **EXAMPLE 41, Step A**. Mass spectrum (ESI): 674.5 (M+1).

<u>**Step B**</u>: <u>7-[(1-*tert*-Butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one</u>

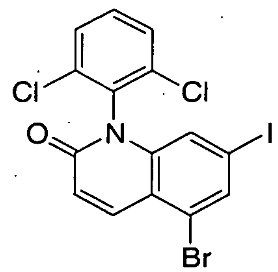
The title compound was prepared from 7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one as described in **INTERMEDIATE 72**. Mass spectrum (ESI): 676.6 (M+1).

<u>**Step C**</u>: <u>7-[(1-*tert*-Butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one</u>

The title compound was prepared from 7-[(1-*tert*-butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one as described in **EXAMPLE ABA1, Step B**. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.53-7.28 (m, 7H); 6.67 (s, 1H); 5.88 (s, 1H); 5.07 (s, 1H); 4.39 (d, J = 14.2 Hz, 1H); 4.23 (d, J = 14.2 Hz, 1H); 2.96 (brd, J = 10.8 Hz, 2H); 2.37 (d, J = 6.2 Hz, 2H); 1.95 (brt, J = 11.1 Hz, 2H); 1.58 (brd, J = 12.6 Hz, 2H); 1.34 (m, 1H); 1.15 (m, 1H); 1.04 (s, 9H). Mass spectrum (ESI): 556.6 (M+1).

INTERMEDIATE ABA4

<u>5-Bromo-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one</u>



Step A: 2,6-Dibromo-4-iodotoluene

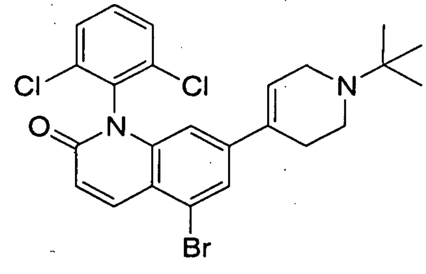
To a solution of 3,5-dibromo-4-methylaniline (4.17g, 15.74mmol) in CH_2I_2 (10mL) was added *tert*-butylnitrite (3.0mL, 23.61mmol) slowly at 0°C while stirring vigorously. The ice bath was removed and the reaction mixture was stirred at rt while the reaction was very exothermic, then placed it in a 80°C oil bath and heated for 20min. CH_2I_2 was distilled off under high vacuum, and the remaining residue was purified by flash chromatography eluting with 100% hexane to gave the title compound.

Step B: 5-Bromo-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one

The title compound was prepared from 2.6-dibromo-4-iodotoluene by procedures analogous to that described in **COMPOUND HHH1** and **COMPOUND HHH2**. ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.2 (d, J = 9.9 Hz, 1H); 7.84 (s, 1H); 7.59-7.45 (m, 3H); 6.87 (d, J = 9.9 Hz, 1H); 6.76 (s, 1H). Mass spectrum (ESI): 496.2 (M+1).

INTERMEDIATE ABA5

5-Bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one

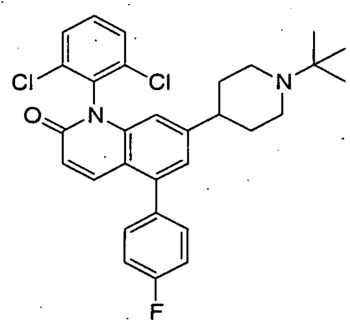


To a solution of 5-bromo-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one (**INTERMEDIATE ABA4**) (541mg, 1.09mmol) in DMF (5mL) was added 1-*tert*-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine (**COMPOUND PPA-2**) (494mg, 1.64mmol) in DMF (5mL). Tetrakis(triphenylphosphine)palladium

(126mg, 0.1mmol) was added to this followed by CuI (156mg, 0.82mmol), and the reaction mixture was purged with argon and stirred at RT. After 18h, it was filtered over Celite® and rinsed thoroughly with EtOAc. The filtrate was washed with H_2O followed by brine and dried over Na_2SO_4. The crude material was purified by flash chromatography eluting with 2% $MeOH/CH_2Cl_2$ to give 315 mg of the title compound. ^1H NMR ($CDCl_3$, 500MHz) of TFA salt: δ 8.24 (d, J = 10 Hz, 1H); 7.56 (m, 1H); 7.46 (m, 1H); 7.25 (m, 1H); 7.17 (m, 1H); 6.87 (d, J = 10 Hz, 1H); 6.32 (s, 1H); 5.88 (m, 1H); 4.20 (m, 1H); 3.76 (m, 1H); 3.53 (m, 1H); 3.11 (m, 1H); 2.87 (m, 1H); 2.44 (m, 1H); 1.47 (s, 9H). Mass spectrum (ESI): 505.3 (M+1).

EXAMPLE ABA11

7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)quinolin-2(1*H*)-one



Step A: 7-(1-*tert*-Butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)quinolin-2(1*H*)-one

The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 4-fluorophenylboronic acid by procedures analogous to that described in **INTERMEDIATE 2**. The title compound was converted to HCl salt by treating it with 2M HCl in Et_2O. Mass spectrum (ESI): 521.5 (M+1).

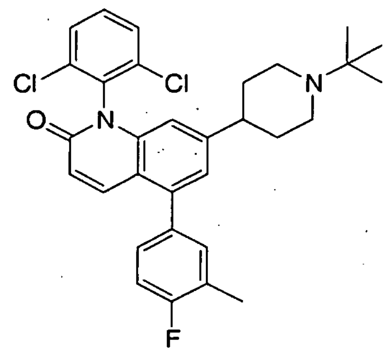
Step B: 7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)quinolin-2(1*H*)-one

The title compound was prepared from HCl salt of 7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)quinolin-2(1*H*)-one (**EXAMPLE ABA11, Step A**) by procedures analogous to that described in **EXAMPLE HHH1, Step B,** as a TFA salt. ^1H NMR (CD_3OD, 500MHz) of TFA

salt: δ 7.97 (d, J = 9.8 Hz, 1H); 7.73 (m, 2H); 7.62 (m, 1H); 7.49 (m, 1H); 7.28 (m, 3H); 6.69 (d, J = 9.8 Hz, 1H); 6.47 (s, 1H); 3.67 (m, 2H); 3.08 (m,2H); 2.96 (m, 1H); 2.1 (m, 2H); 1.99 (m, 2H); 1.42 (s, 9H). Mass spectrum (ESI): 523.3 (M+1).

EXAMPLE ABA12

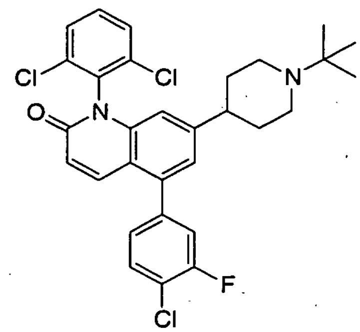
7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluoro-3-methylphenyl)quinolin-2(1*H*)-one



The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 4-fluoro-3-methylphenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.252 (s, 9 H), 1.734 (bs, 2 H), 1.955 (bs, 2 H), 2.084 (s, 3 H), 2.665 (bs, 4 H), 3.307 (m, 1 H), 3.394 (bs, 2 H), 6.471 (s, 1 H), 6.650 (d, J = 9.9 Hz, 1 H), 7.064 (t, J = 5.7 Hz, 1 H), 7.123 (s, 1 H), 7.146 (dd, J = 2.7, 9.9 Hz, 1 H), 7.243 (dd, J = 5.7, 8.5 Hz, 1 H), 7.570 (d, J = 9.9 Hz, 1 H), 7.616 (t, J = 8.5 Hz, 1 H), 7.737 (m, 2 H). Mass spectrum (ESI): 537.2 (M+1).

EXAMPLE ABA13

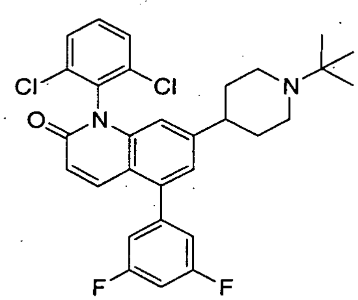
7-(1-*tert*-Butylpiperidin-4-yl)-5-(4-chloro-3-fluorophenyl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one



The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 4-chloro-3-fluorophenylboronic acid as described in **EXAMPLE ABA11.** ^{1}H NMR (CD_3OD, 500 MHz) TFA salt: δ 1.415 (s, 9 H), 1.813 (dd, J = 10.7, 12.8 Hz, 2 H), 2.120 (m, 2 H), 2.947 (tt, J = 3.7, 12.4, 24.7 Hz, 1 H), 3.064 (t, J = 12.8 Hz, 1 H), 3.674 (d, J = 12.6 Hz, 2 H), 6.490 (s, 1 H), 6.736 (d, J = 9.8 Hz, 1 H), 7.245 (s, 1 H), 7.289 (dd, J = 1.6, 8.3 Hz, 1 H), 7.411 (dd, 1.8, 9.8 Hz, 1 H), 7.619 (m, 2 H), 7.728 (m, 2 H), 7.981 (d, J = 9.8 Hz, 1 H). Mass spectrum (ESI): 559.5 (M+1).

EXAMPLE ABA14

7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(3,5-difluorophenyl)quinolin-2(1*H*)-one

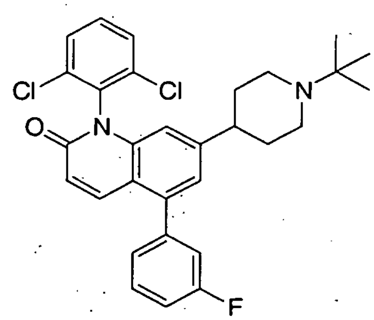


The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 3,5-difluorophenylboronic acid as described in **EXAMPLE ABA11.** ^{1}H NMR (CD_3OD, 500 MHz) TFA salt: δ 1.416 (s, 9 H), 1.827 (m, 2 H), 2.119 (d, J = 14.7 Hz, 2 H), 2.948 (m, 1 H), 3.063 (t, J = 11.0 Hz, 2 H), 3.675 (d, J = 12.6 Hz, 2 H), 6.497 (s, 1 H), 6.747 (d, J = 9.9 Hz, 1 H). 7.122 (m,

3 H), 7.249 (s, 1 H), 7.619 (t, J = 7.6 Hz, 1 H), 7.728 (m, 2 H), 7.987 (d, J = 10.1 Hz, 1 H). Mass spectrum (ESI): 541.5 (M+1).

EXAMPLE ABA15

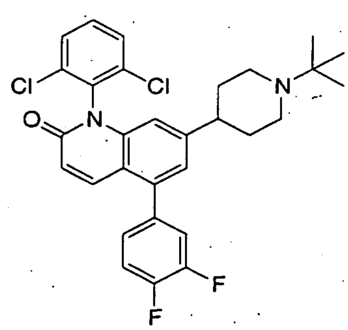
7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(3-fluorophenyl)quinolin-2(1*H*)-one



The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 3-fluorophenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.294 (s, 9 H), 1.756 (bs, 2 H), 2.015 (bs, 2 H), 2.809 (bs, 3 H), 3.447 (bs, 2 H), 6.480 (s, 1 H), 6.713 (d, J = 10.1 Hz, 1 H), 7.245 (m, 4 H), 7.557 (m, 1 H), 7.624 (t, J = 7.6 Hz, 1 H), 7.735 (m, 2 H), 7.986 (d, J = 10.1 Hz, 1 H). Mass spectrum (ESI): 523.5 (M+1).

EXAMPLE ABA16

7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(3,4-difluorophenyl)quinolin-2(1*H*)-one

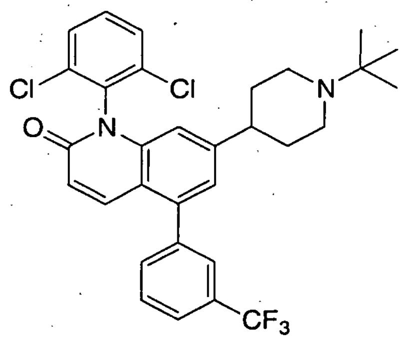


The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one

(**INTERMEDIATE ABA5**) and using 3-fluorophenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD$_3$OD, 500 MHz): δ 1.272 (s, 9 H), 1.700 (bs, 2 H), 1.742 (bs, 2 H), 2.520-2.818 (bs, 3 H), 3.379 (bs, 2 H), 6.478 (s, 1 H), 6.710 (d, J = 10.0 Hz, 1 H), 7.228 (s, 1 H), 7.264 (m, 1 H), 7.420 (m, 2 H), 7.618 (t, J = 7.6 Hz, 1 H), 7.722 (m, 2 H), 7.975 (d, J = 10.0 Hz, 1 H). Mass spectrum (ESI): 541.5 (M+1).

EXAMPLE ABA17

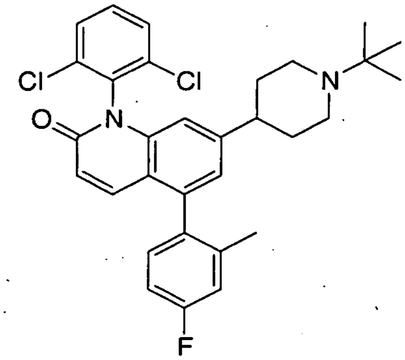
7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-[3-(trifluoromethyl)phenyl]quinolin-2(1*H*)-one



The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 3-trifluoromethylphenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD$_3$OD, 500 MHz) TFA salt: δ 1.358 (s, 9 H), 1.780 (q, J = 10.5, 12.8 Hz, 2 H), 2.062 (d, J = 15.6 Hz, 2 H), 2.702 (m, 1 H), 3.004 (t, J = 13.0 Hz, 2 H), 3.612 (d, J = 13.0 Hz, 2 H), 6.460 (s, 1 H), 6.682 (d, J = 10.2 Hz, 1 H), 7.204 (s, 1 H), 7.565 (t, J = 8.8 Hz, 1 H) 7.672-7.742 (m, 5 H), 7.778 (m, 1 H), 7.844 (d, J = 10.2 Hz, 1 H). Mass spectrum (ESI): 573.5 (M+1).

EXAMPLE ABA18

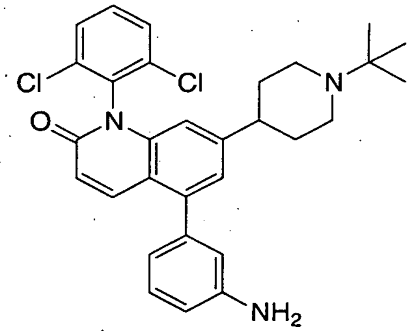
7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluoro-2-methylphenyl)quinolin-2(1*H*)-one



The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 4-fluoro-2-methylphenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.252 (s, 9 H), 1.734 (bs, 2 H), 1.955 (bs, 2 H), 2.384 (s, 3 H), 2.865 (bs, 4 H), 3.497 (m, 2 H), 6.451 (s, 1 H), 6.685 (d, J = 8.5 Hz, 1 H), 7.190 (m, 2 H), 7.265 (m, 1 H), 7.332 (d, J = 8.2 Hz, 1 H), 7.618 (t, J = 8.2 Hz, 1 H), 7.720 (m, 2 H), 7.962 (d, J = 10.7 Hz, 1 H). Mass spectrum (ESI): 537.2 (M+1).

EXAMPLE ABA19

5-(3-Aminophenyl)-7-(1-*tert*-butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one

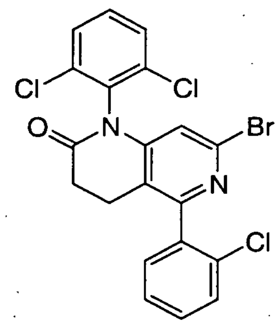


The title compound was prepared from 5-bromo-7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (**INTERMEDIATE ABA5**) and using 3-aminophenylboronic acid as described in **EXAMPLE ABA11**. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.112 (s, 9 H), 1.582 (m, 2 H), 1.814 (m, 2 H), 2.266 (m, 2 H), 2.549 (m, 1 H), 3.139 (m, 2 H), 6.408 (s, 1 H), 6.639 (d, J = 9.9 Hz, 1 H), 6.720 (d, J = 7.3 Hz, 1 H), 6.783 (s, 1 H), 6.813 (d, J = 8.0 Hz, 1

H), 7.181 (s, 1 H), 7.231 (t, J = 7.7 Hz, 1 H), 7.607 (t, J = 7.8 Hz, 1 H), 7.718 (m, 2 H), 8.059 (d, J = 9.9 Hz, 1 H). Mass spectrum (ESI): 520.4 (M+1).

COMPOUND HHH1

7-Bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one



Step A: 4,6-Dibromo-3-(bromomethyl)-2-(2-chlorophenyl)pyridine

To a suspension of 6.3g of 4,6-dibromo-2-(2-chlorophenyl)-3-methylpyridine **(COMPOUND W-1)** in 75mL of CCl_4 was added 3.7g of *N*-bromosuccinimide and 420mg of benzoyl peroxide. The mixture was heated to reflux and stirred at this temperature for 6h, then cooled and concentrated. The residue was dissolved in 150mL of 1:1 hexanes-Et_2O and filtered through a pad of silica gel, then purified in two batches by flash chromatography on Biotage 40M columns, eluting with a gradient system of 99:1 to 97:3 hexanes-Et_2O, to yield the title compound as a white solid.

Step B: *tert*-Butyl 3-[6-bromo-2-(2-chlorophenyl)pyridin-3-yl]propanoate

To 25mL of THF at -78°C was added 26.5mL of a 1.0M solution of lithium hexamethyldisilazane in THF. *t*-Butyl acetate (4.47mL) was added dropwise to the cold solution, and the mixture was stirred for 10min at -78°C. 4,6-Dibromo-3-(bromomethyl)-2-(2-chlorophenyl)pyridine (9.74g) in 25mL of THF was added dropwise over 15min. The mixture was stirred 20min at -78°C, then quenched by addition of 5mL of saturated aqueous $NaHCO_3$. The mixture was warmed to rt, diluted with 200mL of saturated aqueous $NaHCO_3$, and extracted with 3 X 100mL of EtOAc. The combined organics were washed with 100mL of brine, and dried over $MgSO_4$. The residue was purified by flash chromatography on a Biotage 65M column, eluting with a gradient system of 95:5 to 90:10 hexanes-Et_2O to yield the title compound as a white solid. Mass spectrum (ESI) 476 (M+1).

Step C: 3-[6-Bromo-2-(2-chlorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide

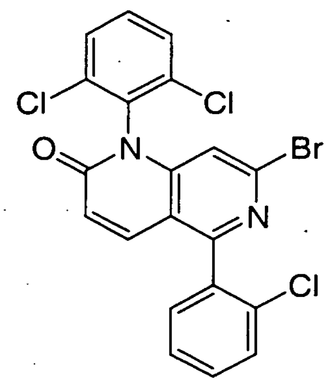
tert-Butyl 3-[6-bromo-2-(2-chlorophenyl)pyridin-3-yl]propanoate (6.82g) in 3.6mL of anisole was dissolved in 25mL of trifluoroacetic acid and the mixture was stirred for 20min at rt, then co-concentrated with 50mL of toluene. The residue was dissolved in 100mL of benzene and 10mL of MeOH and 7.6mL of a 2.0M solution of $TMSCH_2N_2$ was added dropwise. The mixture was stirred 30min at rt; then 2 drops of trifluoroacetic acid were added and then mixture was concentrated. The residue was dissolved in 25mL of CH_2Cl_2. To 2,6-dichloroaniline in 75mL of CH_2Cl_2 was added a 2.0M solution of trimethyl aluminum dropwise. The mixture was stirred 15min at rt; then the methyl ester solution ws added and the mixture was stirred overnight at rt. Water (50mL) was added carefully, then 25mL of Rochelle salt and 50mL of CH_2Cl_2 and the mixture was stirred vigorously for 1h. The mixture was filtered and the solids were dissolved in ca. 500mL of CH_2Cl_2 and washed with 200mL of brine, dried (Na_2SO_4) and concentrated. The filtrate was separated into organic and aqueous phases and the organic phase was washed with 25mL of brine, dried (Na_2SO_4) and concentrated. The combined solids were recrystallized from EtOH to yield the title compound as a white solid. Mass spectrum (ESI) 565 (M+1).

Step D: 7-Bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one

To a suspension of 7.54g of 3-[6-bromo-2-(2-chlorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide in 100mL of DMF was added CuI (3.82g) and powdered, dried K_2CO_3 (3.70g). The mixture was heated to 155°C for 30min, then cooled and diluted with 250mL of half-saturated $NaHCO_3$ and 100mL of EtOAc. The phases were separated and the aqueous phase was extracted 2 x 50mL of EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The reside was purified by flash chromatography on a Biotage 65M column, eluting with a gradient system of 99:1 CH_2Cl_2-acetone to 97:3 CH_2Cl_2-acetone to yield the title compound as an off-white solid. Mass spectrum (ESI) 483 (M+1). ^1H NMR (500 MHz, $CDCl_3$): δ 2.72-2.92 (m, 3H); 2.96-3.06 (m, 1H); 6.37 (s, 1H); 7.39-7.54 (m. 2H); 7.56-7.60 (m, 2H).

COMPOUND HHH2

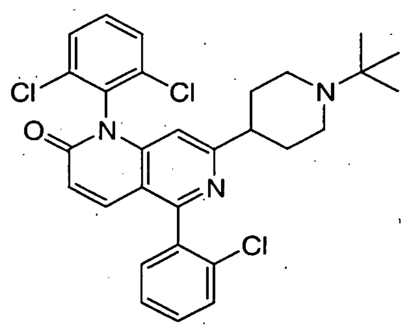
7-Bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



To a solution of 2.31 g of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH1**) in 100mL of CCl_4 was added 40mg of 2,2'azobis(2-methylpropionitrile). The mixture was heated to 80°C; then 940mg of recrystallized *N*-bromosuccinimide was added and the mixture was stirred for 1h at 80°C. DBU (0.72mL) was added and the mixture was cooled to rt. The mixture was washed with 200mL of half-saturated $NaHCO_3$ and the aqueous phase was back-extracted with 100mL of CH_2Cl_2. The combined organics were washed with 100mL of brine, dried (Na_2SO_4), and concentrated to yield the title compound. Mass spectrum (ESI) 481 (M + 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (s, 1H); 6.75 (d, J=10 Hz, 1H); 7.41-7.57 (m. 6H); 7.50-7.65 (m, 2H).

EXAMPLE HHH1

7-(1-*tert*-Butylpiperidin-4-yl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



Step A: 7-(1-*tert*-Butyl-1,2,3,6-tetrahydropyridin-4-yl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

A mixture of 100mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 94mg of 1-

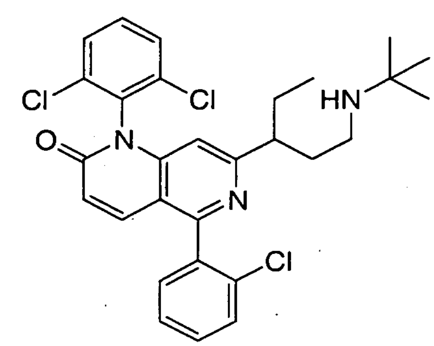
tert-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine (**COMPOUND PPA-2**) in 2mL of dry dioxane was evacuated and purged three times with Ar. $Pd(Ph_3P)_4$ (23mg) was added and the mixture was evacuated and purged again with Ar. The mixture was heated to reflux and stirred at this temperature overnight, then filtered through Celite and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in MeOH, to yield the title compound. The HCl salt was prepared by dissolving this compound in CH_2Cl_2, adding 1eq 1M HCl in Et_2O, and concentrating. Mass spectrum (ESI) 540 (M+1).

<u>Step B</u>: 7-(1-*tert*-Butylpiperidin-4-yl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

To a solution of 75mg of 1-*tert*-butyl-4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-1,2,3,6-tetrahydropyridinium chloride in 3mL of MeOH and 1 mL of EtOAc was added 35mg of PtO_2 (Adam's catalyst). The mixture was evacuated and purged with N_2, then evacuated and purged with H_2, then stirred under an H_2 balloon for 1h. The mixture was filtered through Celite, washing with MeOH, and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in MeOH, followed by preparative HPLC (YMC C8 19x50mm column; 10:90 to 90:10 v/v acetonitrile/water + 0.05% TFA over 12min; 20 mL/minute) to yield the title compound. Mass spectrum (ESI) 542 (M+1). ^1H NMR (500 MHz, CD_3OD): δ 1.40 (s, 9H); 2.04-2.20 (m, 4H); 3.00-3.12 (m, 3H); 3.68 (br d, J=12.5 Hz, 2H); □6.46 (s, 1H); 6.75 (d, J=10 Hz, 1H); 7.48-7.75 (m, 8H).

COMPOUND HHH3

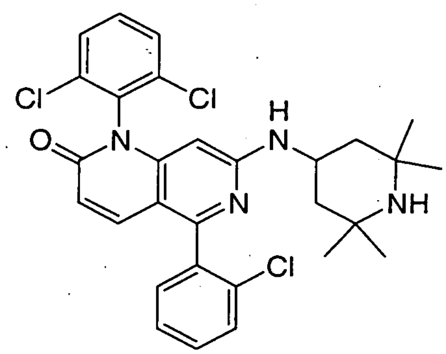
<u>7-[3-(*tert*-Butylamino)-1-ethylpropyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>



7-[3-(*tert*-Butylamino)-1-ethylpropyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one was isolated as a side product in the reduction of 7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**EXAMPLE HHH1**, Step B). Mass spectrum (ESI) 544 (M+1).

COMPOUND HHH4

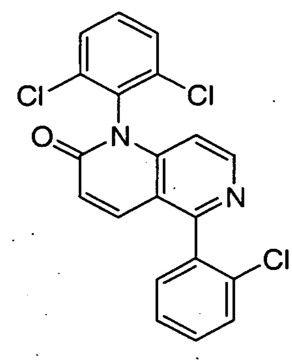
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,6-naphthyridin-2(1*H*)-one



A mixture of 200mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 1mL of 4-amino-2,2,6,6-tetramethylpiperidine in 0.5mL of DMSO was stirred at 130°C for 3h. The mixture was cooled, filtered, and purified by reverse-phase preparative HPLC (YMC C18 100x50mm column; 10:90 to 90:10 v/v acetonitrile/water + 0.1% TFA over 15 min; 20 mL/min) to yield the title compound. Mass spectrum (ESI) 557 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.32-1.58 (m, 14H), 2.05-2.24 (m, 2H), 4.40 (br s, 1H).

COMPOUND HHH5

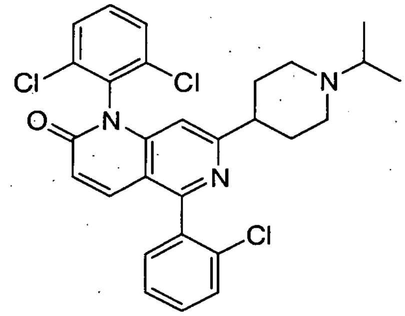
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one was isolated as a side product in the Stille coupling of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 94mg of 1-*tert*-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine (**EXAMPLE HHH1**, Step A). Mass spectrum (ESI) 403 (M+1).

EXAMPLE HHH2

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropylpiperidin-4-yl)-1,6-naphthyridin-2(1*H*)-one



Step A: *tert*-Butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate

The title compound was prepared from 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and *tert*-butyl 4-(trimethylstannyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**INTERMEDIATE 69**)by a procedure analogous to that described in **EXAMPLE HHH1**, Step A. Mass spectrum (ESI) 582 (M+1).

Step B: *tert*-Butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]piperidine-1-carboxylate

The title compound was prepared from *tert*-butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate by a procedure analogous to that described in **EXAMPLE HHH1**, Step B. Mass spectrum (ESI) 586 (M+1).

Step C: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperidin-4-yl-1,6-naphthyridin-2(1*H*)-one

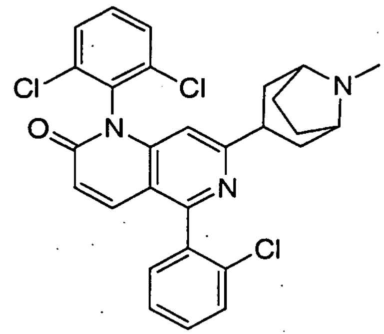
To a solution of 50 mg of *tert*-butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]piperidine-1-carboxylate in 5mL of $CH_2Cl_2$was added 2 mL of trifluoroacetic acid. The mixture was stirred at rt for 1h, then concentrated. The residue was dissolved in 10 mL of CH_2Cl_2, washed with 5mL $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in MeOH, followed by preparative HPLC (YMC C18 20x50mm column; 10:90 to 100:0 v/v acetonitrile/water + 0.1% TFA over 5 min; 20 mL/min) to yield the title compound. Mass spectrum (ESI) 486 (M+1).

Step D: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropylpiperidin-4-yl)-1,6-naphthyridin-2(1*H*)-one

To a solution of 14mg of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperidin-4-yl-1,6-naphthyridin-2(1*H*)-one in 1mL of MeOH was added 0.1mL of acetone, then 9mg of sodium cyanoborohydride. The mixture was stirred 5h at rt, then diluted with 10mL of EtOAc and 10mL $NaHCO_3$. The phases were separated and the aqueous phase was extracted with 2 x 10mL of EtOAc. The combined organics were washed with 10mL of brine, dried (Na_2SO_4), and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in MeOH to yield the title compound. Mass spectrum (ESI) 528 (M+1). ^1H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.07 (d, J=6.5 Hz, 6H), 1.71 (br s, 2H); 1.99 (br s, 2H); 2.26 (br s, 2H); 2.80 (br s, 2H); 3.02 (br s, 2H).

EXAMPLE HHH3

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,6-naphthyridin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1,6-naphthyridin-2(1*H*)-one

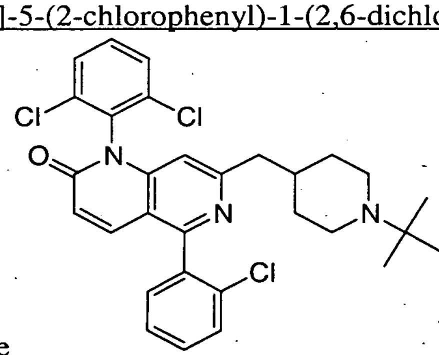
The title compound was prepared from 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 8-methyl-3-(trimethylstannyl)-8-azabicyclo[3.2.1]oct-2-ene (**COMPOUND VV-2**) by a procedure analogous to that described in **EXAMPLE HHH1**, Step A. Mass spectrum (ESI) 524 (M+1).

<u>**Step B**</u>: <u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,6-naphthyridin-2(1*H*)-one</u>

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-1,6-naphthyridin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE HHH1**, Step B. Mass spectrum (ESI) 526 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.19 (s, 6H); 1.26 (s, 6H); 2.17 (s, 2H); 6.62 (s, 1H).

EXAMPLE HHH4

<u>7-[(1-*tert*-Butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>



<u>**Step A**</u>: <u>7-[(1-*tert*-Butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>

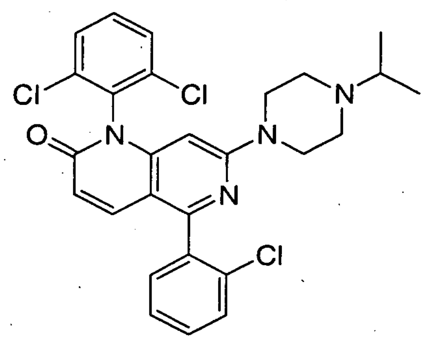
The title compound was prepared from 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 1-*tert*-butyl-4-[(trimethylstannyl)methylene]piperidine (**INTERMEDIATE ABA3**)by a procedure analogous to that described in **EXAMPLE HHH1**, Step A. Mass spectrum (ESI) 554 (M+1).

Step B: 7-[(1-*tert*-Butylpiperidin-4-yl)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

The title compound was prepared from 7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE HHH1**, Step B. Mass spectrum (ESI) 556 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.38 (s, 9H); 1.45-1.60 (m, 2H); 1.88-2.10 (m, 2H); 2.78 (br d, J=7 Hz, 2H); 2.87-2.97 (m, 2H); 3.58 (br d, J=12 Hz, 2H).

EXAMPLE HHH5

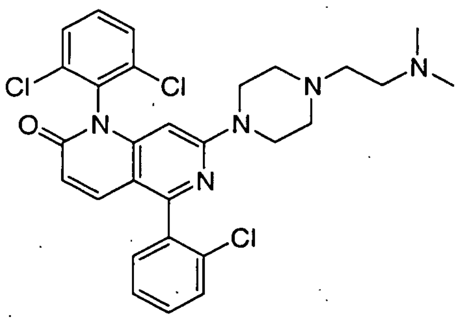
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(4-isopropylpiperazin-1-yl)-1,6-naphthyridin-2(1*H*)-one



The title compound was prepared from 50mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 1 mL of 1-isopropylpiperazine by a procedure analogous to that described in **COMPOUND HHH4**. Mass spectrum (ESI) 529 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.04 (d, J=6.5 Hz, 6H); 2.55 (br s, 4H); 2.70 (m, 1H); 3.49 (br s, 4H).

EXAMPLE HHH6

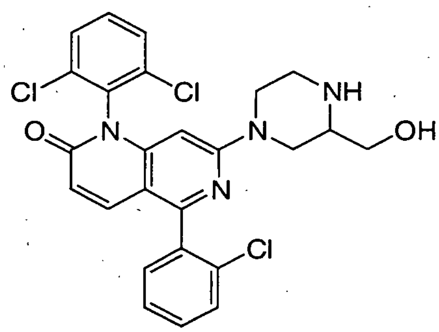
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-1,6-naphthyridin-2(1*H*)-one



The title compound was prepared from 50mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 1mL of *N,N*-dimethyl-2-piperazin-1-ylethanamine by a procedure analogous to that described in **COMPOUND HHH4**. Mass spectrum (ESI) 558 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 2.94 (s, 6H); 3.23 (m, 4H); 3.44 (t, J=7.5 Hz, 2H); 3.56 (t, J=6.5 Hz, 2H); 3.76 (m, 4H).

EXAMPLE HHH7

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[3-(hydroxymethyl)piperazin-1-yl]-1,6-naphthyridin-2(1*H*)-one



Step A: 7-[3-(*tert*-Butoxymethyl)piperazin-1-yl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

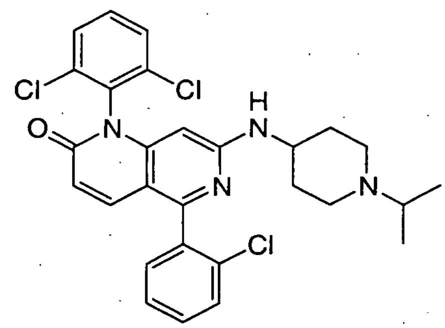
The title compound was prepared from 25mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**), 46mg of 2-(*tert*-butoxymethyl)piperazinediium diacetate, and 40μL of diisopropyl ethylamine by a procedure analogous to that described in **COMPOUND HHH4**. Mass spectrum (ESI) 573 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[3-(hydroxymethyl)piperazin-1-yl]-1,6-naphthyridin-2(1*H*)-one

To 25mg of 7-[3-(*tert*-butoxymethyl)piperazin-1-yl]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one was added 1mL of TFA. The mixture was stirred 2h at rt, then concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 9:1 CH_2Cl_2-2M NH_3 in MeOH. Mass spectrum (ESI) 517 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 2.78-3.02 (m, 4H); 3.09 (br d, J=12 Hz, 1H); 3.59 (m, 1H); 3.68 (dd, J=3.5, 10.5 Hz, 1H); 3.84 (br d, J=12 Hz, 1H); 4.05 (br d, J=13 Hz, 1H).

EXAMPLE HHH8

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-isopropylpiperidin-4-yl)amino]-1,6-naphthyridin-2(1*H*)-one



Step A: *tert*-Butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]amino}piperidine-1-carboxylate

The title compound was prepared from 50mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 63mg of *tert*-butyl 4-aminopiperidine-1-carboxylate by a procedure analogous to that described in **COMPOUND HHH4**. Mass spectrum (ESI) 599 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylamino)-1,6-naphthyridin-2(1*H*)-one

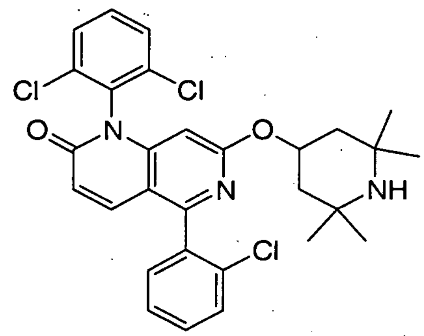
The title compound was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]amino}piperidine-1-carboxylate by a procedure analogous to that described in **EXAMPLE HHH2**, Step C. Mass spectrum (ESI) 501 (M+1).

Step C : 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-isopropylpiperidin-4-yl)amino]-1,6-naphthyridin-2(1*H*)-one

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylamino)-1,6-naphthyridin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE HHH2**, Step D. Mass spectrum (ESI) 543 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.03 (d, J=6 Hz, 6H); 1.50 (m, 2H); 1.96 (m, 2H); 2.21 (m, 2H); 2.68-2.85 (m, 3H); 3.34 (br s, 1H).

COMPOUND HHH6

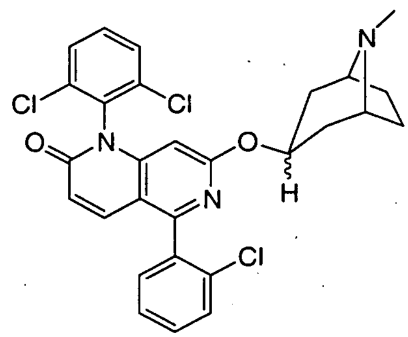
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]-1,6-naphthyridin-2(1*H*)-one



To a solution of 82mg of 2,2,6,6-tetramethylpiperidin-4-ol in 1mL of DMSO was added 13mg of NaH. The mixture was stirred 15min at rt; then 50mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) was added and the mixture was stirred at 50°C for 4h, then cooled and quenched by addition of 0.1mL water plus one drop of TFA. The mixture was filtered and purified by reverse-phase preparative HPLC (YMC C18 20x100mm column; 10:90 to 100:0 v/v acetonitrile/water + 0.1% TFA over 15min; 20mL/min) to yield the title compound. Mass spectrum (ESI) 556 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3H); 1.38 (s, 3H); 1.40 (s, 3H), 1.41 (s, 3H); 2.09 (m, 2H); 2.18 (m, 2H); 3.50 (s, 0.6H); 5.53 (m, 1H); 5.57 (s, 1H); 6.54 (d, J=10 Hz, 1H); 7.38-7.63 (m, 8H).

EXAMPLE HHH9

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-1,6-naphthyridin-2(1*H*)-one



Step A: Tropine and Pseudotropine

To a 3.7mL of a 1M solution of lithium aluminum hydride in 16mL of THF was added a solution of tropinone in 5mL of THF dropwise over ca. 10min. The mixture was stirred 30min at rt, then quenched by careful addition of 0.14mL of water, 0.14mL of 15% aqueous NaOH, and 0.52mL of water. The mixture was stirred vigorously for 15min, then filtered, washing liberally with CH_2Cl_2 and concentrated to yield a ca. 1.4:1 mixture of pseudotropine and tropine. Mass spectrum (ESI) 142 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-1,6-naphthyridin-2(1*H*)-one

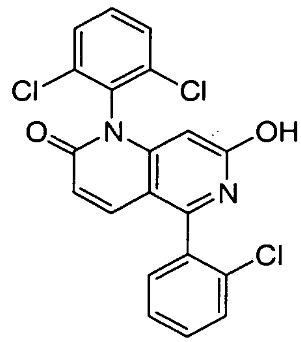
The title compound was prepared from 100mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**), 147mg of a ca. 1.4:1 mixture of pseudotropine and tropine (**EXAMPLE HHH9**, Step A), and 25 mg of NaH by a procedure analogous to that described in **COMPOUND HHH6**.

Diastereomer 1 (from pseudotropine): Mass spectrum (ESI) 542 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.63 (m, 2H); 1.83 (m, 2H); 2.00 (m, 4H); 2.36 (s, 3H); 3.24 (br s, 2H); 5.35 (m, 1H).

Diastereomer 2 (from tropine): Mass spectrum (ESI) 542 (M+1).). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 2.00-2.30 (m, 6H); 2.35-2.65 (m, 5H); 3.30 (br s, 2H); 5.39 (m, 1H).

COMPOUND HHH7

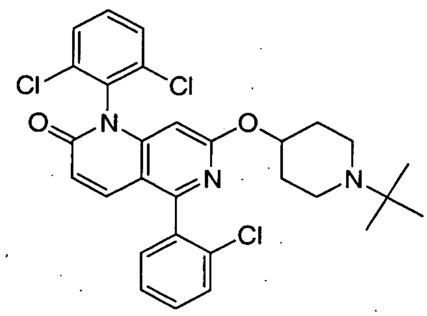
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-1,6-naphthyridin-2(1*H*)-one



5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-1,6-naphthyridin-2(1*H*)-one was isolated as a side product in the coupling of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and a mixture of pseudotropine and tropine (**EXAMPLE HHH9**, Step B). Mass spectrum (ESI) 419 (M+1).

EXAMPLE HHH10

7-[(1-*tert*-Butylpiperidin-4-yl)oxy]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



Step A: 1-*tert*-Butylpiperidin-4-ol

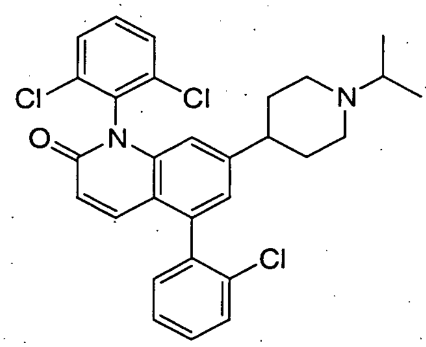
To a 0°C solution of 1.0g of 1-*tert*-butylpiperidin-4-one (**COMPOUND PPA-1**) in 2mL of THF was added 6.4mL of a 1M solution of lithium aluminum hydride in THF dropwise. The mixture was stirred 10min at rt, then quenched by careful addition of 0.2mL of water, 0.2mL of 15% aqueous NaOH, and 0.6mL of water. The mixture was stirred vigorously for 30min, then filtered and concentrated to yield the title compound.

Step B: 7-[(1-*tert*-Butylpiperidin-4-yl)oxy]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

The title compound was prepared from 40mg of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**), 55mg of 1-*tert*-butylpiperidin-4-ol, and 8 mg of NaH by a procedure analogous to that described in **COMPOUND HHH6**. Mass spectrum (ESI) 556 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$; doubling of peaks due to restricted rotation) δ 1.44 and 1.42 (2 s, 9H); 2.20-2.53 (m, 4H); 2.77 (m, 0.6H); 3.05 (br s, 1.6H); 3.50 (m, 1.5H); 3.70 (m, 0.8H); 4.60-5.40 (m, 2.9H); 5.39 (br s, 0.8H); 5.75 and 5.80 (2 s, 1H); 6.54 and 6.56 (2 d, J=8.5 Hz and J=10 Hz, 1H); 7.36-7.66 (m, 8H).

EXAMPLE HHH11

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropylpiperidin-4-yl)quinolin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxyquinolin-2(1*H*)-one (INTERMEDIATE 7) by a procedure analogous to that described in **EXAMPLE 1**, Step A.

Step B: *tert*-Butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl trifluoromethanesulfonate by a procedure analogous to that described in **EXAMPLE 1**, Step B. Mass spectrum (ESI) 583 (M+1).

Step C: *tert*-Butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-1-carboxylate

The title compound was prepared from *tert*-butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-3,6-

dihydropyridine-1(2*H*)-carboxylate by a procedure analogous to that described in **EXAMPLE HHH2**, Step B. Mass spectrum (ESI) 585 (M+1).

Step D: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperidin-4-ylquinolin-2(1*H*)-one

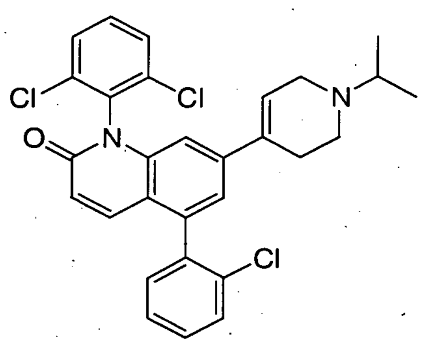
The title compound was prepared from *tert*-butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate by a procedure analogous to that described in **EXAMPLE HHH2**, Step C. Mass spectrum (ESI) 483 (M+1).

Step E: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropylpiperidin-4-yl)quinolin-2(1*H*)-one

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-piperidin-4-ylquinolin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE HHH2**, Step D. Mass spectrum (ESI) 527 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (br s, 6H); 1.42-1.96 (m, 4H); 2.10-3.20 (m, 6H); 6.38 (s, 1H); 6.65 (d, J=10 Hz, 1H); 7.34-7.62 (m, 7H).

EXAMPLE HHH12

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1*H*)-one



Step A: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1*H*)-one

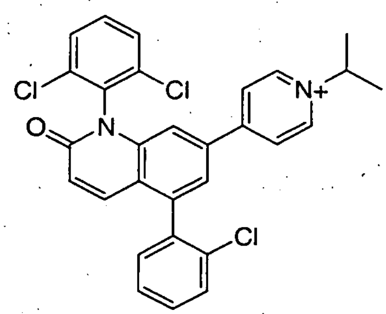
The title compound was prepared from *tert*-butyl 4-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate by a procedure analogous to that described in **EXAMPLE HHH2**, Step C. Mass spectrum (ESI) 482 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1*H*)-one

The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE HHH2**, Step D. Mass spectrum (ESI) 525 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ

COMPOUND HHH8

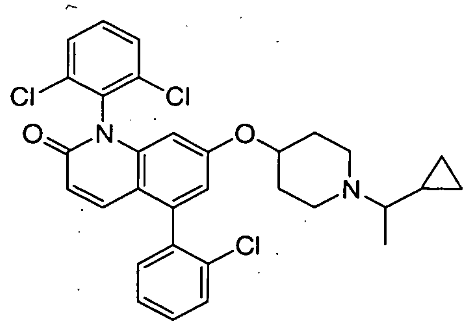
4-[5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-1-isopropylpyridinium



4-[5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]-1-isopropylpyridinium was a minor product in the reductive amination of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1*H*)-one (**EXAMPLE HHH12**, Step B). Mass spectrum (ESI) 519 (M+).

EXAMPLE HHH13

5-(2-Chlorophenyl)-7-{[1-(1-cyclopropylethyl)piperidin-4-yl]oxy}-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one



Step A: *tert*-Butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]oxy}piperidine-1-carboxylate

The title compound was prepared from 55mg 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxyquinolin-2(1*H*)-one (**INTERMEDIATE 9**), 500mg of polymer-bound Ph_3P, 128 mg of *tert*-butyl 4-hydroxypiperidine-1-carboxylate, and 122mg of diethyl azodicarboxylate by a procedure analogous to that described in **EXAMPLE 2**. Mass spectrum (ESI) 599 (M+1).

<u>Step B</u>: <u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-yloxy)quinolin-2(1*H*)-one</u>

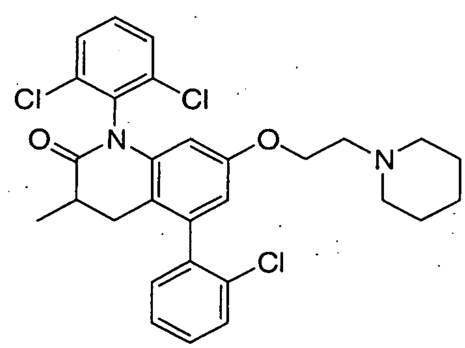
The title compound was prepared from *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinolin-7-yl]oxy}piperidine-1-carboxylate by a procedure analogous to that described in **EXAMPLE HHH2**, Step C. Mass spectrum (ESI) 499 (M+1).

<u>Step C</u>: <u>5-(2-Chlorophenyl)-7-{[1-(1-cyclopropylethyl)piperidin-4-yl]oxy}-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one</u>

To a solution of 8.8mg of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-yloxy)quinolin-2(1*H*)-one in 0.9mL of MeOH was added 0.1mL of 1-cyclopropylethanone, then 6.5mg of sodium cyanoborohydride. The mixture was stirred 4d at rt. Another 0.5mL of 1-cyclopropylethanone was added and the mixture was heated to reflux overnight, then concentrated and purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in MeOH to yield the title compound. Mass spectrum (ESI) 567 (M+1).

EXAMPLE HHH14

<u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3-methyl-7-(2-piperidin-1-ylethoxy)-3,4-dihydroquinolin-2(1*H*)-one</u>



<u>Step A</u>: <u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one</u>

To 1mL of THF at -78°C was added 130μL of a 1M solution of lithium bis(trimethylsilyl)amide in THF, then a solution of 50mg of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxyquinolin-2(1*H*)-one (**INTERMEDIATE 6**) in 2mL of THF dropwise. The mixture was stirred for 30min at -78°C; then 57mg of methyl iodide was added dropwise. The mixture was stirred 10min at -78°C, then removed from the bath and allowed to warm to rt. The reaction was quenched by addition of 100μL of MeOH, then poured into 10mL of water and extracted with 2 x 10mL of CH_2Cl_2. The combined organics were washed with 10mL of brine, dried ($MgSO_4$), and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-acetone, to yield a 1:1.5 mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxyquinolin-2(1*H*)-one and the title compound. Mass spectrum (ESI) 446 (M+1).

Step B: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one

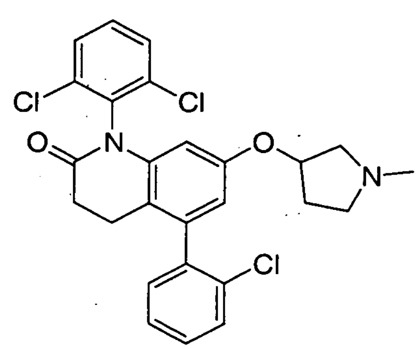
The title compound was prepared from 43mg of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-methoxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one by a procedure analogous to that described in **INTERMEDIATE 3.**

Step C: 5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-3-methyl-7-(2-piperidin-1-ylethoxy)-3,4-dihydroquinolin-2(1*H*)-one

The title compound was prepared from 7mg of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one, 40mg of Ph_3P, 20μL of 1-piperidine ethanol, and 20μL of diethyl azodicarboxylate by a procedure analogous to that described in **EXAMPLE** 2. Mass spectrum (ESI) 545 (M+1).

EXAMPLE RRR-1

5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-methylpyrrolidin-3-yl)oxy]-3,4-dihydroquinolin-2(1*H*)-one



<u>**Step A**:</u> <u>Benzyl 3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl]oxy}pyrrolidine-1-carboxylate</u>

A solution of 0.046 g of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-hydroxy-3,4-dihydro-1-quinolin-2(1*H*)-one (**INTERMEDIATE 6**), triphenylphosphine (0.086g), and (R)-3-hydroxy-N-Boc-pyrrolidine (0.062g) in 8mL of THF was heated to 65°C. DEAD (87μL) was added dropwise over 2min and the mixture was stirred at rt for 1h. Purification was achieved by preparative thin layer chromatography eluting with 50% ethyl acetate/hexanes to give 0.051g. Mass spectrum *m/z* (ESI) 587.2 (M+1).

<u>**Step B**:</u> <u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-(pyrrolidin-3-yloxy)-3,4-dihydroquinolin-2(1*H*)-one</u>

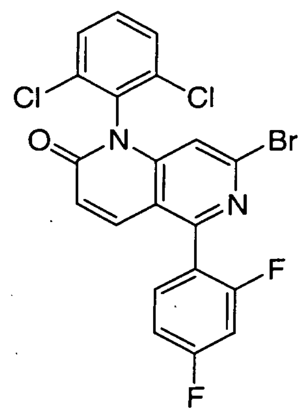
To a solution of benzyl 3-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl]oxy}pyrrolidine-1-carboxylate (0.051g) in 6mL of CH_2Cl_2 was added 1mL of TFA and the mixture was stirred for 1h at rt. The reaction mixture was purified by preparative thin layer chromatography eluting with 10% ethanol/dichloromethane to give the product. Mass spectrum *m/z* (ESI) 487.15 (M+1).

<u>**Step C**:</u> <u>5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-methylpyrrolidin-3-yl)oxy]-3,4-dihydroquinolin-2(1*H*)-one</u>

To a solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(pyrrolidin-3-yloxy)-3,4-dihydroquinolin-2(1*H*)-one (0.046g) in 5mL of methanol was added formaldehyde (50μL) and sodium cyanoborohydride (0.012g). The reaction mixture was stirred for 48h, then washed with 1N HCl (5mL), extracted with 5 x 5mL of ethyl acetate, washed with brine (5mL), dried with sodium sulfate, and concentrated. Purification was achieved by preparative thin layer chromatography eluting with 10% ethanol/dichloromethane to yield product. Mass spectrum (ESI) 501.1 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.48 (m, 3H), 7.36-7.30 (m, 4H), 6.38 (s, 1H), 5.85 (s, 1H), 4.66 (m, 1H), 2.87-2.65 (m, 8H), 2.36 (s, 3H), 2.18-2.15 (m, 1H), 1.94-1.91 (m, 1H).

COMPOUND RRR-1

<u>7-Bromo-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>



Step A: 2-(2,4-difluorophenyl)-3-methyl-5-nitropyridine

To a stirred solution of 2-chloro-3-methyl-5-nitropyridine (prepared according to the procedure of Hawkins and Roe, J. Am. Chem. Soc., page 330, 1948) (17.6g, 102mmol, 1eq.) in DMF (220mL) was added 2,4-difluorobenzeneboronic acid (16.16g, 102mmol, 1eq.) followed by Cs_2CO_3 (41.1g, 122.7mmol, 1.2eq). The mixture was degassed with argon. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (2.5g, 2mmol, 0.02eq). The mixture was degassed with argon and then heated to 100°C under argon. After 18h the mixture was cooled.. The mixture was filtered and the filtrate concentrated under reduced pressure. The filtrate was partitioned between water and ethyl acetate. The aqueous layer was extracted several times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The material was purified by flash column chromatography eluting with 5:1 hexanes/acetone giving 7.5 g 2-(2,4-difluorophenyl)-3-methyl-5-nitropyridine. Mass spectrum (ESI) 251.3 (M+1). ^1H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 9.35 (1H, s); 8.42 (1H, s); 7.47 (1H, m); 7.07 (1H, m); 6.97 (1H, m); 2.41 (3H, s).

Step B: 6-(2,4-difluorophenyl)-5-methylpyridin-3-amine

To a stirred solution of 2-(2,4-difluorophenyl)-3-methyl-5-nitropyridine (7.5g, 30mmol, 1eq) in methanol (100mL) in a 500mL round bottom flask was added 7g of Raney Nickel slurry. The flask was evacuated and charged with hydrogen 4 times. The mixture was stirred under H_2. After 5h the reaction flask was purged with nitrogen. The mixture was filtered and the methanol was removed under reduced pressure giving 6.4 g 6-(2,4-difluorophenyl)-5-methylpyridin-3-amine. Mass spectrum (ESI) 221.3 (M+1).

Step C: 2,4-dibromo-6-(2,4-difluorophenyl)-5-methylpyridin-3-amine

To a stirred solution of (2,4-difluorophenyl)-5-methylpyridin-3-amine (6.4g, 29.3mmol, 1eq) in THF (20mL) was added 2N aqueous HCl (40mL). The mixture was cooled to 0°C and bromine (4.6mL, 89.28mmol, 3eq) was added dropwise via syringe. There was noticeable warming of the reaction mixture. The cooling bath was removed and the mixture was stirred 6h. The reaction was quenched by addition of aqueous $NaHSO_3$. Ethyl acetate was added to the mixture and aqueous layer made basic to effect dissolution of the solids. The mixture was extracted 3x with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated giving 2,4-dibromo-6-(2,4-difluorophenyl)-5-methylpyridin-3-amine. Mass spectrum (ESI) 377.2 (M+1); 379.2 (M+3); 381.2 (M+5). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 7.39 (1H m); 6.98 (1H, m); 6.88 (1H, m); 4.69 (2H, br s); 2.25 (3H, s).

Step D: 4,6-dibromo-2-(2,4-difluorophenyl)-3-methylpyridine

To a stirred solution of 2,4-dibromo-6-(2,4-difluorophenyl)-5-methylpyridin-3-amine (10g, 26.4mmol, 1eq) in THF (100mL) was added *tert*-butylnitrite (4.7mL, 39.6mmol, 1.5eq). The solution warmed and gas evolution was evident. After 2h, the mixture was heated to and maintained at 60°C for 45min. The mixture was cooled and concentrated in vacuo. The product was purified by flash column chromatography eluting with 2% Et_2O in hexanes to give 4,6-dibromo-2-(2,4-difluorophenyl)-3-methylpyridine. Mass spectrum (ESI) 362.2 (M+1); 364.2 (M+3); 366.2 (M+5).

Step E: 4,6-dibromo-3-(bromomethyl)-2-(2,4-difluorophenyl)pyridine

To a stirred solution of 4,6-dibromo-2-(2,4-difluorophenyl)-3-methylpyridine (5.0g, 13.77mmol, 1eq) in CCl_4 (125mL) was added N-bromosuccinimide (2.95g, 16.6mmol 1.2eq) and benzoyl peroxide (340mg, 1.37mmol, 0.1eq). The mixture was brought to and maintained at reflux until all the starting material was consumed (approx 3.5h). The reaction mixture was cooled to 0°C and the succinimide was filtered off. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel eluting with 2% Et_2O in hexanes giving 4,6-dibromo-3-(bromomethyl)-2-(2,4-difluorophenyl)pyridine. Mass spectrum (ESI) 440.1 (M+1); 442.1 (M+3); 444.1 (M+5); 446.1 (M+7). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 7.84 (1H, s); 7.50 (1H, m); 7.05 (1H, m); 6.96 (1H, m); 4.44 (2H br s).

Step F: *tert*-Butyl 3-[4,6-dibromo-2-(2,4-difluorophenyl)pyridin-3-yl]propanoate

To a –78°C solution of the lithium bis(trimethylsilylamide) (14mL) in 3mL of THF was added t-butylacetate (2mL). After stirring for 10min, 4,6-dibromo-

2-(2,4-difluorophenyl)-3-methylpyridine (1.0g) dissolved in 3mL THF was added dropwise. The mixture stirred at –78°C for 1.5h, then warmed to –50°C. The reaction mixture was then recooled to –78°C and 3mL of methanol was added. The solution stirred for 24h at rt. The crude mixture was purified by flash chromatography, eluting with 50% ethyl acetate/hexanes. Mass spectrum *m/z* (ESI) 478.3 (M+1).

Step G: 3-[4,6-Dibromo-2-(2,4-difluorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide

A solution of *tert*-butyl 3-[4,6-dibromo-2-(2,4-difluorophenyl)pyridin-3-yl]propanoate (3.56g) in 20mL of TFA was stirred for 45min at rt, then co-concentrated with 40mL of toluene. The resulting oil was dissolved in 50mL of benzene and 5mL of MeOH. Trimethylsilyldiazomethane (6mL) was added dropwise and the mixture was stirred for 30min, then quenched by addition of 1mL of TFA, then concentrated to an off-white solid. To a solution of 2,6-dichloroaniline (2.42g) in 40mL of CH_2Cl_2 was added dropwise 7.5mL of trimethylaluminum; this mixture was stirred for 15min. The methyl ester was dissolved in 40mL of CH_2Cl_2 and added to the 2,6-dichloroaniline mixture. After stirring for 24h at rt, water was carefully added. A solution of 25mL of Rochelle salt and 25mL of CH_2Cl_2 was added and the mixture was stirred for 1h at rt. A white solid precipitated and was filtered. The remaining solid was dissolved in CH_2Cl_2 and extracted with brine, dried with sodium sulfate and concentrated to yield the amide. Mass spectrum *m/z* (ESI) 562.8 (M+1).

Step H: 7-Bromo-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one

To a solution of 3-[4,6-dibromo-2-(2,4-difluorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide (1g) in 30mL of DMF was added potassium carbonate (0.489g) and copper iodide (0.5g). The reaction mixture was stirred for 24h at 155°C, then cooled and diluted with 10mL of saturated sodium bicarbonate. This solution was extracted twice with 10mL of ethyl acetate, washed with 10mL of brine, dried with sodium sulfate, then concentrated. The residue was purified by flash chromatography with 1% acetone in CH_2Cl_2. Mass spectrum *m/z* (ESI) 485.3 (M+1).

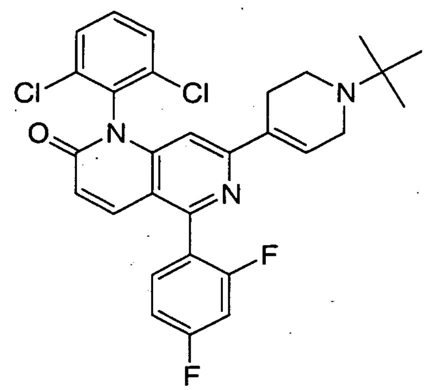
Step I: 7-Bromo-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one

To a refluxing solution of 7-bromo-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (0.747g) and AIBN (0.03g) in 30mL of CCl_4 was added recrystallized *N*-bromosuccinimide (0.302g). The reaction was stirred at reflux for 1h, then removed from the heat. DBU (0.23mL) was

added and the mixture was stirred at rt for 15min. The reaction mixture was washed with 100mL of saturated sodium bicarbonate and back extracted with 50mL of dichloromethane. The combined organics were washed with 100mL of brine, dried with sodium sulfate, and concentrated to give the desired product. Mass spectrum *m/z* (ESI) 481.3 (M+1).

EXAMPLE RRR-2

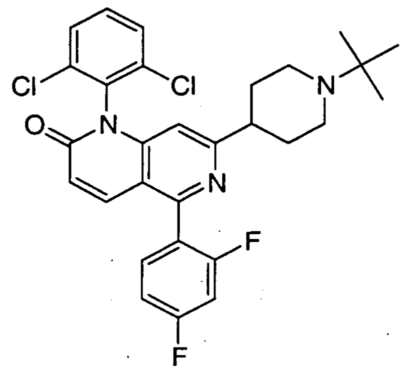
7-(1-*tert*-Butyl-1,2,3,6-tetrahydropyridin-4-yl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



To a solution of 0.10g of 7-bromo-5-(2,4-difluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND RRR-1**) in 5mL of dioxane was added 0.083g of 1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-trimethyltin (**COMPOUND PPA-2**) dissolved in 1mL of dioxane. The solution was purged with argon; then tetra(triphenylphosphine)palladium (0.053g) was added and the mixture was heated to 100°C for 7h. The product was purified by preparative thin layer chromatography eluting with 50% ethyl acetate/hexanes, then by high pressure liquid chromatography (flow rate = 20mL/min., gradient = 10% - 100% acetonitrile [0.05% TFA] in water [0.05% TFA] over 12min, column = XTerra C8 19x50mm). Mass spectrum (ESI) 540.5 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J=10Hz 1H), 7.59 (m, 3H), 7.46 (t, J=4Hz, 1H), 7.09 (t, J=4Hz, 1H), 6.99 (t, J=4Hz, 1H), 6.71 (d, J=10Hz, 1H), 6.63 (s, 1H), 6.31 (s, 1H), 3.34 (s, 2H), 2.73 (s, 2H), 2.48 (s, 2H), 1.06 (s, 9H).

EXAMPLE RRR-3

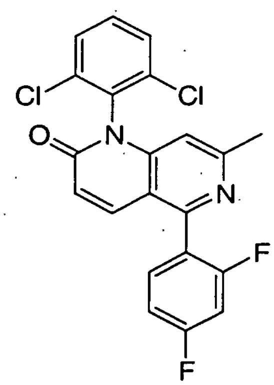
7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



To a solution of 0.0237g of 7-bromo-5-(2,4-difluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND RRR-1**) in 5mL of 9:1 methanol-ethyl acetate was added platinum oxide (0.0115g). The mixture was stirred under a hydrogen balloon for 30min, then filtered and purified by high pressure liquid chromatography (flow rate = 20mL/min., gradient = 10% - 100% acetonitrile [0.05% TFA] in water [0.05% TFA] over 12min, column = XTerra C8 19x50mm), then by preparative thin layer chromatography. Mass spectrum (ESI) 542.4 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J=10 Hz, 1H), 7.59 (m, 3H), 7.46 (t, J=4 Hz, 1H), 7.09 (t, J=4 Hz, 1H), 6.99 (t, J=4 Hz,1H), 6.71 (d, J=10 Hz, 1H), 6.28 (s, 1H), 3.15 (br s, 2H), 2.74 (m, 1H), 2.20 (br s, 2H), 1.97 (br s, 2H), 1.64 (br s, 2H), 1.05 (s, 9H).

COMPOUND RRR-3

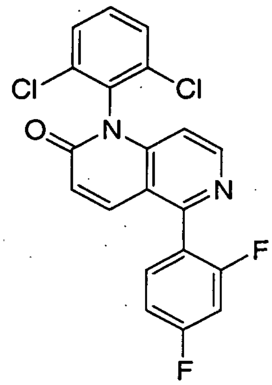
<u>1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-methyl-1,6-naphthyridin-2(1*H*)-one</u>



The title compound was a minor product in the coupling of 7-bromo-5-(2,4-difluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one) and 1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-trimethyltin (**EXAMPLE RRR-2**). Mass spectrum (ESI) 417.3 (M+1).

COMPOUND RRR-4

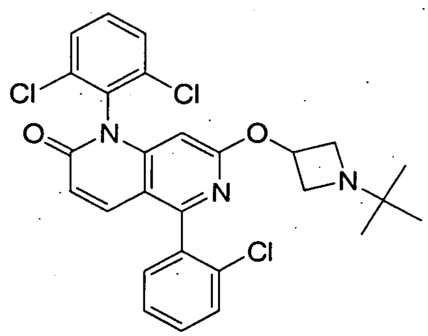
1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



The title compound was a minor product in the coupling of 7-bromo-5-(2,4-difluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one) and 1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-trimethyltin (**EXAMPLE RRR-2**). Mass spectrum (ESI) 403.2 (M+1).

EXAMPLE RRR-4

7-[(1-*tert*-Butylazetidin-3-yl)oxy]-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one

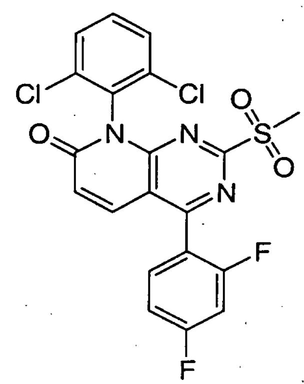


To a solution of *N*-*tert*-butylazetidin-4-ol (prepared as described by V. Gaertner, *Tetrahedron Lett.* **1966**, 4691.)) in 5mL of dioxane was added sodium hydride (0.005g). The mixture was stirred at rt for 10min; then 0.05g of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH1**) was added and the mixture was heated to reflux and stirred at this temperature for 3h. Purification of the product was achieved by preparative thin layer

chromatography eluting with 10% methanol/dichloromethane. Mass spectrum (ESI) 528.04 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.62 (m, 3H), 7.51-7.39 (m, 5H), 6.54 (d, J=6Hz, 1H), 5.79 (s, 1H), 5.28 (m, 1H), 3.89 (br s, 2H), 3.44 (br s, 2H), 1.09 (s, 9H).

COMPOUND RRR-5

8-(2,6-Dichlorophenyl)-4-(2,4-difluorophenyl)-2-(methylsulfonyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



Step A: *tert*-Butyl 3-[4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]propanoate

To a –78°C solution of LiHMDS (4.1mL) in 3mL of THF was added *t*-butylacetate (0.6mL). After stirring for 10min, 1.0g of 5-(bromomethyl)-4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidine (**COMPOUND VV-3**) in 4mL of THF was added dropwise. The mixture was stirred at –78°C for 1.5h, then warmed to –50°C. The reaction mixture was recooled to –78°C and 3mL of methanol was added. The solution stirred for 24h at rt. The crude mixture was purified by flash chromatography, eluting with 2% diethyl ether/hexanes. Mass spectrum *m/z* (ESI) 401.5 (M+1).

Step B: 3-[4-Chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]-*N*-(2,6-dichlorophenyl)propanamide

A solution of *tert*-butyl 3-[4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]propanoate (1.0g) in 5mL of TFA was stirred for 45min at rt, then co-concentrated with 10mL of toluene. The resulting oil was dissolved in 15mL of benzene and 2mL of MeOH. Trimethylsilyldiazomethane (1.3mL) was added dropwise and the mixture was stirred for 30min; then 0.5mL of TFA was added and the mixture was concentrated to an off-white solid. To a solution of 2,6-

dichloroaniline (0.8g) in 10mL of CH_2Cl_2 was added dropwise 2.5mL of trimethylaluminum, and the mixture was stirred 15min. The methyl ester was dissolved in 10mL of CH_2Cl_2 and added to the 2,6-dichloroaniline mixture. After stirring for 24h at rt, water was carefully added. A solution of 5mL of Rochelle salt and 10mL CH_2Cl_2 was added and the mixture was stirred for 1h at rt. A white solid precipitated and was filtered. The filtrate was extracted with brine, dried with sodium sulfate and concentrated to give the amide. Mass spectrum *m/z* (ESI) 488.3 (M+1).

<u>Step C:</u> <u>3-[4-Chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]-*N*-(2,6-dichlorophenyl)propanamide</u>

To a solution of 3-[4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]-*N*-(2,6-dichlorophenyl)propanamide (0.28g) in 15mL of dimethylformamide was added potassium carbonate (0.237g) and copper iodide (0.218g). The reaction mixture was stirred for 24h at 150°C, then cooled and diluted with 5mL of saturated sodium bicarbonate. This solution was extracted twice with 5mL of ethyl acetate, washed with 5mL of brine, dried with sodium sulfate, then concentrated. Purification was achieved by high pressure liquid chromatography (flow rate = 20mL/min, gradient = 90% - 10% water (0.01% TFA) in acetonitrile over 15min, column = YMC C18 100x20mm). Mass spectrum *m/z* (ESI) 452.4 (M+1).

<u>Step D:</u> <u>8-(2,6-Dichlorophenyl)-4-(2,4-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one</u>

To a refluxing solution of 3-[4-chloro-6-(2,4-difluorophenyl)-2-(methylthio)pyrimidin-5-yl]-*N*-(2,6-dichlorophenyl)propanamide (0.06g) and AIBN (0.005g) in 8mL of CCl_4 was added recrystallized *N*-bromosuccinimide (0.026g). The reaction was refluxed for 1h, then removed from the heat. DBU (0.02mL) was added and the solution was stirred at rt for 15min. The reaction mixture was washed with 20mL of saturated sodium bicarbonate and back extracted with 20mL of CH_2Cl_2. The organic layer was washed with 20mL of brine, dried with sodium sulfate, and concentrated to give the desired product. Mass spectrum *m/z* (ESI) 450.4 (M+1).

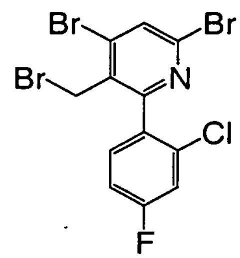
<u>Step E:</u> <u>8-(2,6-Dichlorophenyl)-4-(2,4-difluorophenyl)-2-[(trifluoromethyl)sulfonyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one</u>

To a solution of 8-(2,6-dichlorophenyl)-4-(2,4-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.022g) in 1 mL of THF was added MMPP (0.048g). The reaction mixture was stirred for 1h at rt, then diluted with 5mL of ethyl acetate and filtered through Celite. This filtrate was washed with saturated sodium bicarbonate and back extracted with CH_2Cl_2. The combined organics were washed with brine, dried with sodium sulfate, and concentrated. The product was

obtained by preparative thin layer chromatography eluting with 5% acetone/dichloromethane. Mass spectrum *m/z* (ESI) 482.3 (M+1).

COMPOUND PS

4,6-dibromo-3-(bromomethyl)-2-(2-chloro-4-fluorophenyl)pyridine



STEP A: 2-(2-chloro-4-fluorophenyl)-3-methyl-5-nitropyridine

To a stirred solution of 2-chloro-3-methyl-5-nitropyridine (prepared according to the procedure of Hawkins and Roe, J. Am. Chem. Soc., page 330, 1948) (5.3g, 30.7mmol, 1eq.) in 1,2-dimethoxyethane (50mL) and ethanol (25mL) was added 2-chloro-4-fluorobenzeneboronic acid (5.9g, 33.8mmol, 1.1eq.). The resulting mixture was degassed with argon. To the mixture was added a solution of Na_2CO_3 (11.4g, 107.45mmol, 3.5eq) in water (50mL). The mixture was degassed with argon, and tetrakis(triphenylphosphine)palladium(0) (1.1g, 0.95mmol, 0.03eq) was added. The mixture was degassed with argon and heated to 90°C under argon. After 4.5h, the mixture was cooled. The solvent was removed under reduced pressure. The residue was diluted with water and extracted 3x with ethyl acetate. The aqueous layer was extracted several times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography on silica gel eluting with 5% Et_2O in hexanes giving 2-(2-chloro-4-fluorophenyl)-3-methyl-5-nitropyridine. Mass spectrum (ESI) 267 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 9.35 (1H, d, J=2.2Hz); 8.42(1H, d, J=2.2Hz); 7.3 (2H, m); 7.16 (1H, m); 2.32 (3H, s).

STEP B: 6-(2-chloro-4-fluorophenyl)-5-methylpyridin-3-amine

A 250mL round bottom flask was charged with 2-(2-chloro-4-fluorophenyl)-3-methyl-5-nitropyridine (4g) and methanol (50mL). To the flask was added Raney nickel/methanol slurry (approx 4g). The flask was evacuated and charged with hydrogen several times. The mixture was stirred under a balloon of hydrogen for 2.5h. The flask was purged with nitrogen. The catalyst was filtered off and the filtrate was concentrated under reduced pressure giving 6-(2-chloro-4-

fluorophenyl)-5-methylpyridin-3-amine as an off white solid. Mass spectrum (ESI) 237 (M+1).

STEP C: 2,4-dibromo-6-(2-chloro-4-fluorophenyl)-5-methylpyridin-3-amine

To a solution of 6-(2-chloro-4-fluorophenyl)-5-methylpyridin-3-amine (3.33g, 14.11mmol, 1eq) in THF (10mL) was added 2N aqueous HCl (20 mL). To this mixture was added bromine (2.17g, 42.33mmol, 3eq) dropwise via syringe. The mixture was stirred 6h and then quenched by addition of aqueous $NaHSO_3$. The mixture was made basic and then extracted 3x with isopropyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated to give 2,4-dibromo-6-(2-chloro-4-fluorophenyl)-5-methylpyridin-3-amine. Mass spectrum (ESI) 393 (M+1); 395 (M+3); 397 (M+5). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 7.30 (1H, dd, J=6.2Hz, J=8.5Hz); 7.21 (1H, dd, J=8.5Hz, J=2.5Hz); 7.07 (1H, ddd, J= 8.5Hz, J=8.5Hz, J=2.5Hz); 4.7 (2H, br s); 2.18 (3H, s).

Step D: 4,6-dibromo-2-(2-chloro-4-fluorophenyl)-3-methylpyridine

To a stirred solution of 2,4-dibromo-6-(2-chloro-4-fluorophenyl)-5-methylpyridin-3-amine (4.8 g, 12.2mmol, 1eq) in THF (50mL) was added *tert*-butylnitrite (2.2 mL, 18.25mmol, 1.5eq). The mixture was warmed to 60°C and mild gas evolution was observed. After 1.75h the heating bath was turned off and the mixture was allowed to stir overnight. Additional *tert*-butylnitrite (1mL) was added and the mixture was again warmed to 60 °C. After 2h no starting material was left as assessed by HPLC analysis. The mixture was cooled and the solvent removed under reduced pressure. The product was purified by flash column chromatography on silica gel eluting with 2% Et_2O in hexanes to give 4,6-dibromo-2-(2-chloro-4-fluorophenyl)-3-methylpyridine. Mass spectrum (ESI) 378.0 (M+1); 380.0 (M+3); 382.0 (M+5).

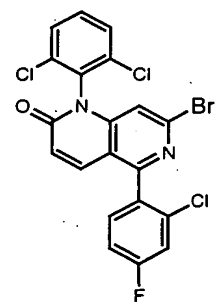
Step E: 4,6-dibromo-3-(bromomethyl)-2-(2-chloro-4-fluorophenyl)pyridine

To a solution of 4,6-dibromo-2-(2-chloro-4-fluorophenyl)-3-methylpyridine (3.55g, 9.35mmol, 1eq) in 1,2-dichloroethane (90mL) was added N-bromosuccinimide (2.0g, 11.22 mmol, 1.2 eq) and benzoyl peroxide (226 mg, 0.9mmol, 0.1eq). The resulting mixture was degassed with argon then warmed to and maintained at reflux for 5.5h. The mixture was cooled. solvent was removed under reduced pressure, and the material was purified by flash column chromatography eluting with 2% Et_2O in hexanes. The material was re-dissolved in CCl_4 and N-bromosuccinimide (667mg) and benzoyl peroxide (75mg) were added. The mixture was brought to and maintained at reflux for 6.5h. The mixture was cooled to 0°C, filtered to remove the succinimide, and concentrated under reduced pressure. The

product was purified by flash column chromatography on silica gel eluting with 2% Et2O in hexanes to give 4,6-dibromo-3-(bromomethyl)-2-(2-chloro-4-fluorophenyl)pyridine. Mass spectrum (ESI) 456.1 (M+1); 458.0 (M+3); 460.1 (M+5); 462.1 (M+7). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta CHCl_3$: 7.85 (1H, s); 7.46 (1H, dd, J= 8.5Hz, J=5.7Hz); 7.27 (1H, dd, J=8.5Hz, J=2.5Hz); 7.16 (1H, ddd, J= 8.5 Hz, J=8.3Hz, J=2.5Hz); 4.55 (1H, ½ ABq, J= 10.8Hz); 4.17 (1H, ½ ABq, J=10.8 Hz).

COMPOUND CCC1

7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



STEP A: *tert*-butyl 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-yl]propanoate

To a 1M solution of lithium bis(trimethlsilyl)amide (10.5 mL) at –78 °C was added *tert*-butyl acetate (1.77 mL, 13.2 mmol) dropwise. To this mixture a solution of 4,6-dibromo-3-(bromomethyl)-2-(2-chloro-4-fluorophenyl)pyridine (4.02g, 8.77mmol) (**COMPOUND PS**) in 9.2mL of THF was added dropwise over 20min. After stirring for 30min at –78°C, the reaction mixture was quenched by the dropwise addition of 3mL of methanol, then warmed up to rt and partitioned between 30mL each of saturated aqueous $NaHCO_3$ and ethyl acetate. The aqueous phase was extracted with 2 x 20mL of ethyl acetate. The combined organic layers were washed with brine (20mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with warm Et_2O. The mother liquor was purified by flash chromatography on a Biotage 40M column eluting with 97:3 hexanes-ethyl acetate. The two batches were combined to give the *tert*-butyl 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-yl]propanoate. Mass spectrum (ESI) 492.4 (M+1).

STEP B: 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide

tert-butyl 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-

yl]propanoate (3.42g, 6.93mmol) was dissolved in 12mL of trifluoroacetic acid and stirred at rt for 0.75h. 30mL of toluene was added and the resulting mixture was concentrated under reduced pressure. The resulting solid was dissolved in 50mL of benzene and 5mL of methanol. A 2M solution of (trimethylsilyl)diazomethane in hexanes (4.16mL, 8.32mmol) was added dropwise and the reaction mixture was stirred for 30min. 2 drops of trifluoroacetic acid were added and the solvent was removed under reduced pressure. The resulting methyl ester was dissolved in 12mL of CH_2Cl_2. To 2,6-dichloroaniline (2.25g, 13.9mmol) in 36mL of CH_2Cl_2 was added dropwise a 2M solution of trimethylaluminum in toluene (7.0mL, 13.9mmol) and the mixture was stirred for 15min. Then the methyl ester solution in CH_2Cl_2 was added and the resulting mixture was stirred at rt overnight. 24mL of water was added very carefully followed by 12mL of an aqueous 1M solution of potassium sodium tartarate and 24mL of CH_2Cl_2. The mixture was stirred vigorously for 1h and then filtered. The filtered solids were dissolved with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give one pure crop. The filtrate was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with hot ethanol to give a second pure crop. The two crops were combined to give the 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide as a white solid. Mass spectrum (ESI) 579.2 (M+1).

STEP C: 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one

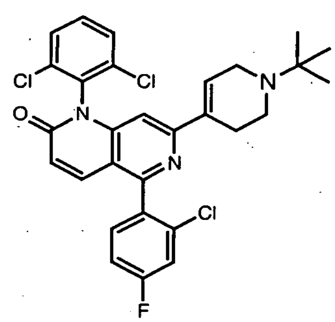
To 3-[4,6-dibromo-2-(2-chloro-4-fluorophenyl)pyridin-3-yl]-*N*-(2,6-dichlorophenyl)propanamide (3.14g, 5.40mmol) in DMF (50mL) was added K_2CO_3 (1.49g, 10.8mmol) and CuI (1.54g, 10.8mmol). The resulting reaction mixture was evacuated and purged with argon 3 times, and then heated at 155°C (oil bath) for 35min. The reaction mixture was cooled to rt and diluted with 240mL of half-saturated aqueous $NaHCO_3$ and 120mL of ethyl acetate. The layers were separated and the aqueous layer was extracted with 2 x 180mL of ethyl acetate. The combined organic layers were washed with 120mL of brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography on 2 Biotage 40M columns, eluting with 50:50 hexanes-CH_2Cl_2 to yield 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one. Mass spectrum (ESI) 499.2 (M+1).

STEP D: 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

To 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (2.33g, 4.65mmol) in 75mL of CCl_4 was added recrystallized *N*-bromosuccinimide (993mg, 5.58mmol) and 2,2'azobis(2-methylpropionitrile) (76.4mg, 0.465mmol). The resulting reaction mixture was evacuated and flushed with argon 3 times, then heated and maintained at reflux for 2.5h. 1,8-diazabicyclo[5.4.0]undec-7-ene (695μL, 4.65mmol) was added and the reaction mixture was cooled to rt, washed with 140mL of half-saturated aqueous $NaHCO_3$, and the aqueous layer was back-extracted with 2 x 70mL of ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography on Biotage 40M column, eluting with a gradient system of 90:10 hexanes-ethyl acetate to 80:20 hexanes-ethyl acetate to yield 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one as an off white solid. Mass spectrum (ESI) 497 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (s, 1H); 6.79 (d, J=10.1 Hz, 1H); 7.21 (m, 1H), 7.31 (m, 1H); 7.54 (m, 3H); 7.65 (m, 2H).

EXAMPLE CZC1

7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

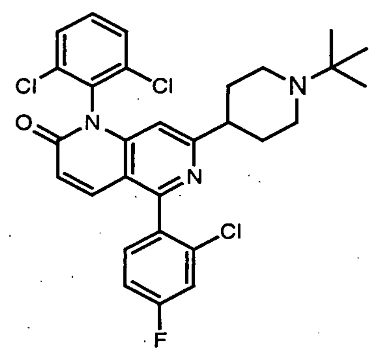


To 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (100mg, 0.20mmol) **(COMPOUND CCC1)** in anhydrous 1,4-dioxane (5 mL) was added 1-*tert*-butyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine (91mg, 0.30mmol) **(COMPOUND PPA2)**. The reaction mixture was evacuated and purged three times with argon. Then tetrakis(triphenylphosphine)palladium(0) (35mg, 0.03mmol) was added and the mixture was evacuated and purged again with argon. The mixture was heated and maintained at reflux overnight. The mixture was cooled to rt, diluted with ethyl

acetate, filtered through a pad of Celite, and concentrated under reduced pressure. The product was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in methanol to yield the title compound. Mass spectrum (ESI) 556.4 (M+1). ^{1}H NMR (400 MHz, CD_3OD): δ 1.13 (s, 9H); 2.46 (brs, 2H); 2.78 (t, J=5.2Hz, 2H), 3.35 (brs, 2H); 6.45 (s, 1H); 6.72 (m, 2H); 7.31 (ddd, J=8.3 Hz, J=8.3 Hz, J=2.6 Hz, 1H); 7.46 (dd, J=8.8 Hz, J=2.5 Hz, 1H); 7.56 (dd, J=8.6 Hz, J=6 Hz, 1H); 7.65 (m, 2H); 7.75 (m, 2H).

EXAMPLE CCC1

7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

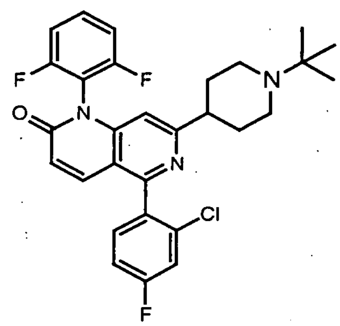


To 1-*tert*-butyl-4-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-1,2,3,6-tetrahydropyridinium chloride (682mg, 1.15mmol) (prepared by diluting 7-(1-*tert*-butyl-1,2,3,6-tetrahydropyridin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**EXAMPLE CZC1**) with CH_2Cl_2, adding 1eq of a 2M solution of HCl in Et_2O, and concentrating under reduced pressure) in 24mL of 9:1 methanol-ethyl acetate was added 341mg of PtO_2 (Adam's catalyst) under nitrogen. The reaction flask was evacuated and charged with hydrogen several times and stirred for 0.75h under hydrogen. The flask was purged with nitrogen and the reaction mixture was filtered through a pad of Celite washing with methanol and concentrated under reduced pressure. The product was purified by flash chromatography on a Biotage 40L column, eluting with a gradient of 100:0 CH_2Cl_2-methanol to 95:5 CH_2Cl_2-methanol, followed by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 60:40 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 27min, at 20mL per minute) to yield the title compound as the trifluoroacetate salt. Mass spectrum

(ESI) 558.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.38 (s, 9H); 2.12 (m, 4H); 3.03 (brs, 3H); 3.65 (d, J=12.1, 2H); 6.47 (s, 1H); 6.76 (d, J=9.9 Hz, 1H); 7.32 (ddd, J=8.5 Hz, J=8.5 Hz, J=2.5 Hz, 1H); 7.48 (dd, J=8.7 Hz, J=2.5 Hz, 1H); 7.57 (dd, J=8.4 Hz, J=6.2 Hz, 1H); 7.66 (t, J=8.3 Hz, 1H); 7.70 (d, J=9.8Hz, 1H); 7.75 (m, 2H).

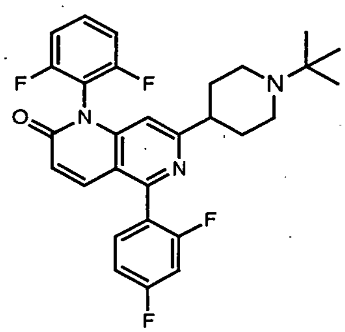
EXAMPLE CCC1-A

7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



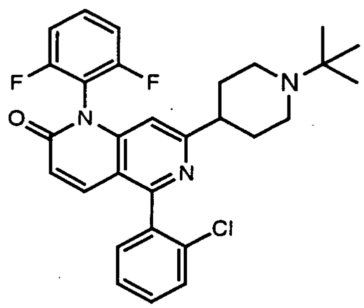
EXAMPLE CCC1-B

7-(1-*tert*-butylpiperidin-4-yl)-5-(2,4-difluorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



EXAMPLE CCC1-C

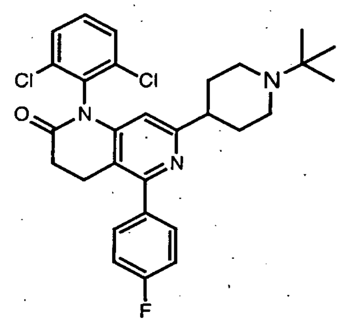
7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chlorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one



By procedures similar to that for **EXAMPLE CCC1**, **EXAMPLE CCC1-A:** 7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one, **EXAMPLE CCC1-B:** 7-(1-*tert*-butylpiperidin-4-yl)-5-(2,4-difluorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one, and **EXAMPLE CCC1-C:** 7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chlorophenyl)-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one can be made.

EXAMPLE CCC2

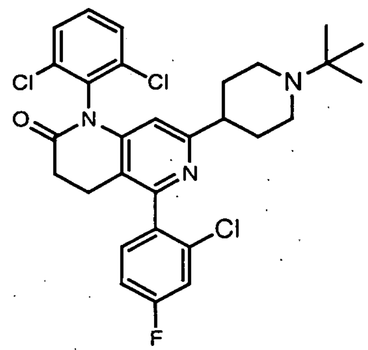
7-(1-*tert*-butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one



7-(1-*tert*-butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(4-fluorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one was isolated as a side product in the reduction of 1-*tert*-butyl-4-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-1,2,3,6-tetrahydropyridinium chloride (**EXAMPLE CCC1**). Mass spectrum (ESI) 526.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.40 (s, 9H); 2.04 (m, 2H); 2.13 (d, J=13 Hz, 2H); 2.84 (t, J=6.9 Hz, 2H); 2.97 (m, 1H); 3.05 (m, 2H); 3.18 (t, J=7.1 Hz, 2H); 3.68 (d, J=12.3 Hz, 2H); 6.12 (s, 1H); 7.28 (t, J=8.7 Hz, 2H); 7.58 (t, J=7.5 Hz, 1H); 7.66 (m, 4H).

EXAMPLE CCC3

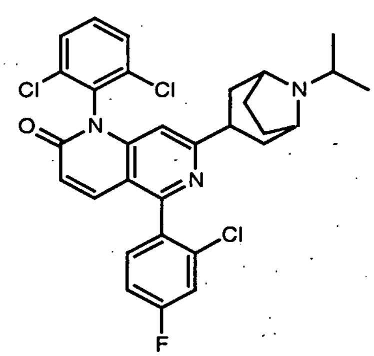
7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one



7-(1-*tert*-butylpiperidin-4-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one was isolated as a side product in the reduction of 1-*tert*-butyl-4-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-1,2,3,6-tetrahydropyridinium chloride (**EXAMPLE CCC1**). Mass spectrum (ESI) 560.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.11 (s, 9H); 1.61 (m, 2H); 1.87 (m, 2H); 2.30 (m, 2 H); 2.65 (m, 1H); 2.88 (m, 4H); 3.16 (d, J=10.5 Hz, 2H); 6.17 (s, 1H); 7.26 (ddd, J=8.4 Hz, J=8.4 Hz, J=2.5 Hz, 1H); 7.42 (dd, J=8.7 Hz, J=2.6 Hz, 1H); 7.49 (dd, J=8.5 Hz, J=6.1 Hz, 1H); 7.58 (t, J=8 Hz, 1H); 7.68 (d, J=8.5 Hz, 1H).

EXAMPLE CCC4

5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-1,6-naphthyridin-2(1*H*)-one



STEP A: *tert*-butyl 3-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

The *tert*-butyl 3-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate was prepared from 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND CCC1**) and *tert*-butyl 3-(trimethylstannyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**COMPOUND PPA-3**) by a procedure analogous to that described in **EXAMPLE CZC1**, except that the eluting solvents in the purification step were 20:80 acetone-hexanes. Mass spectrum (ESI) 626 (M+1).

STEP B: 7-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

tert-butyl 3-[5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (103mg) was dissolved in 1mL of trifluoroacetic acid and stirred under nitrogen at rt for 0.75h. The resulting reaction mixture was concentrated under reduced pressure and purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in methanol to yield 7-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one. Mass spectrum (ESI) 526 (M+1).

STEP C: 7-(8-azabicyclo[3.2.1]oct-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one

39mg of PtO_2 (Adam's catalyst) was added to the mixture of 7-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (77mg) in 2mL ethyl acetate. The resulting reaction mixture was evacuated and purged with argon. Then hydrogen was bubbled through and the reaction mixture was stirred under hydrogen for 8h. The reaction mixture was filtered, concentrated under reduced pressure, and purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in methanol to yield 7-(8-azabicyclo[3.2.1]oct-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one. Mass spectrum (ESI) 528.6 (M+1).

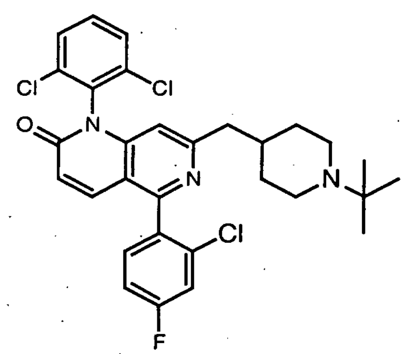
STEP D: 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-1,6-naphthyridin-2(1*H*)-one

To a mixture of 7-(8-azabicyclo[3.2.1]oct-3-yl)-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (36mg, 0.068mmol) in 1mL of 1,2-dichloroethane was added 0.6mL acetone and 4 drops of acetic acid. The resulting reaction mixture was stirred under nitrogen for 30min and $NaBH(OAc)_3$ (145mg, 0.68mmol) was added. The reaction was stirred at rt for 14days, then quenched with 2M aqueous NaOH and extracted 3 times with ethyl

acetate. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The product was purified twice by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in methanol followed by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 60:40 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 27min, at 20mL/min) to yield 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-7-(8-isopropyl-8-azabicyclo[3.2.1]oct-3-yl)-1,6-naphthyridin-2(1*H*)-one as the trifluoroacetate salt. Mass spectrum (ESI) 570 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.31 (m, 6H); 6.61 (d, J=24.5 Hz, 1H); 6.77 (d, J=9.8 Hz, 1H); 7.33 (ddd, J=8.5 Hz, J=8.5 Hz, J=2.5 Hz, 1H); 7.50 (dd, J=8.7 Hz, J=2.6 Hz, 1H); 7.57 (m, 1H); 7.67 (m, 2H); 7.75 (d, J=8.0 Hz, 2H).

EXAMPLE CCC5

<u>7-[(1-*tert*-butylpiperidin-4-yl)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>



STEP A: <u>7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>

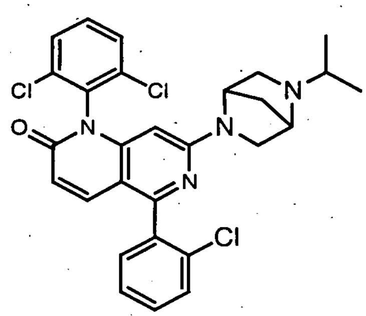
The 7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one was prepared from 7-bromo-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND CCC1**) and 1-*tert*-butyl-4-[(trimethylstannyl)methylene]piperidine (**INTERMEDIATE ABA3**) by a procedure analogous to that described in **EXAMPLE CZC1**. Mass spectrum (ESI) 570 (M+1).

STEP B: <u>7-[(1-*tert*-butylpiperidin-4-yl)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one</u>

The 7-[(1-*tert*-butylpiperidin-4-yl)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one was prepared from 7-[(1-*tert*-butylpiperidin-4-ylidene)methyl]-5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE CCC4, STEP C**, except that the purification was done by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 60:40 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 25min, at 20Ml/min) to give the trifluoroacetate salt. Mass spectrum (ESI) 572.7 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.38 (s, 9H); 1.51 (m, 2H); 1.93 (d, J=14.4 Hz, 2H); 2.05 (m, 1H); 2.78 (d, J=7.3 Hz, 2H); 2.92 (m, 2H); 3.58 (d, J=12.2 Hz, 2H).

EXAMPLE CCC6

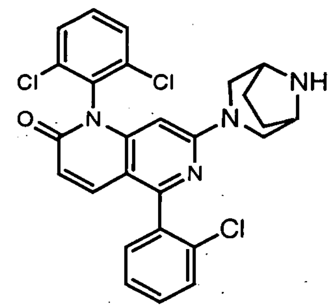
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (26 mg, 0.054 mmol) (**COMPOUND HHH2**) and 2-isopropyl-2,5-diazabicyclo[2.2.1]heptane (**INTERMEDIATE ABA2**) (11mg, 0.078mmol) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 25h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) followed by preparative thin-layer chromatography, eluting with 90:10 CH_2Cl_2-2M NH_3 in methanol to yield the title compound. Mass spectrum (ESI) 539.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 1.05 (d, J=6.2 Hz, 6H); 1.87 (m, 2H); 2.53 (m, 2H); 3.01 (m, 1H); 3.18 (d, J=8.5 Hz, 1H); 3.3 (brs, 1H); 3.81 (s, 1H); 4.7 (brs, 1H); 5.25 (s, 1H); 6.30 (d, J=9.6 Hz, 1H); 7.42 (d, J=9.7 Hz, 1H); 7.49 (m, 3H); 7.59 (m, 2H); 7.71 (m, 2H).

EXAMPLE CCC7

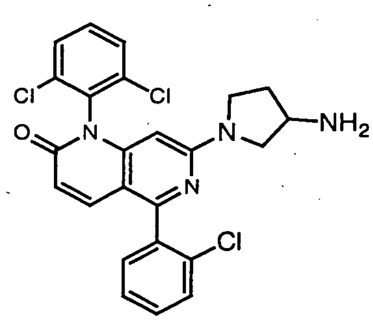
5-(2-chlorophenyl)-7-(3,8-diazabicyclo[3.2.1]oct-3-yl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (81mg, 0.17mmol) (**COMPOUND HHH2**), 3,8-diazabicyclo[3.2.1]octane dihydrochloride (62mg, 0.34mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (65mg, 0.43mmol) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 10.2h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 511 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 2.02 (m, 4H); 3.17 (d, J=12.1 Hz, 2H); 4.13 (m, 4H).

EXAMPLE CCC8

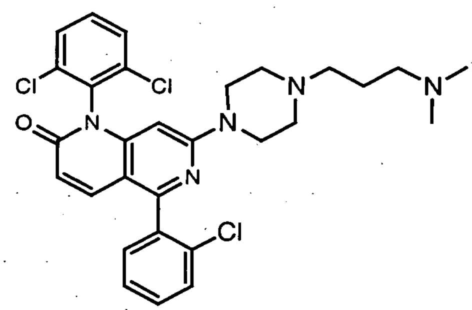
7-(3-aminopyrrolidin-1-yl)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (80mg, 0.17mmol) (**COMPOUND HHH2**), pyrrolidin-3-amine dihydrochloride (135mg, 0.85mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (259mg, 1.7mmol) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 7h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) followed by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-2M NH_3 in methanol to yield the title compound. Mass spectrum (ESI) 485 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.76 (m, 1H); 2.16 (m, 1H); 3.11 (brs, 1H); 3.40 (brs, 1H); 3.57 (brs, 2H); 3.68 (m, 1H).

EXAMPLE CCC9

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-1,6-naphthyridin-2(1*H*)-one

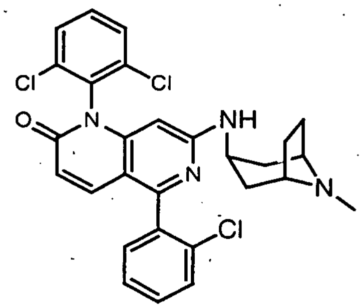


A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40mg, 0.083mmol) (**COMPOUND HHH2**) and *N,N*-dimethyl-3-piperazin-1-ylpropan-1-amine (72mg, 0.42mmol) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 6.5h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) The trifluoroacetate salt was partitioned between 2M aqueous NaOH and ethyl acetate and the water layer extracted with ethyl acetate twice. The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to yield the title compound. Mass spectrum (ESI) 570 (M+1). ^{1}H NMR (500 MHz, CD_3OD):

selected peaks δ 2.20 (m, 2H); 2.91 (s, 6H); 3.20 (m, 5H); 3.36 (brs, 4H); 3.81 (brs, 3H).

EXAMPLE CCC10

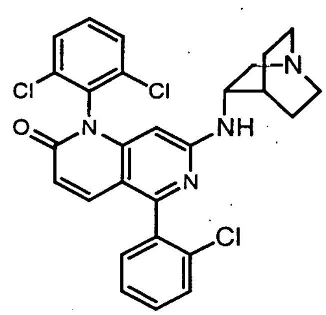
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (80mg, 0.17mmol) (**COMPOUND HHH2**) and 8-methyl-8-azabicyclo[3.2.1]octan-3-amine (279mg, 1.99mmol) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 29h. The mixture was cooled to rt, filtered, and purified twice by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 539 (M+1). ^1H NMR (500 MHz, CD_3OD): selected peaks δ 2.30 (m, 8H); 2.75 (s, 3H); 3.83 (brs, 2H); 4.08 (brs, 1H).

EXAMPLE CCC11

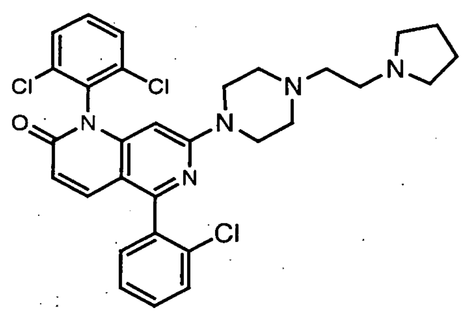
7-(1-azabicyclo[2.2.2]oct-3-ylamino)-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40 mg, 0.083 mmol) (COMPOUND HHH2), quinuclidin-3-amine dihydrochloride (84 mg, 0.42 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (70 mg, 0.46 mmol) in 0.5 mL of DMSO was stirred under nitrogen at 130 °C for 6.5 hours. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15 minutes, at 20 mL per minute) to yield 24 mg of the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 525.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 5.66 (m, 1H); 6.41 (d, J=9.6 Hz, 1H); 7.49 (m, 4H); 7.61 (m, 2H); 7.30 (d, J=8.4 Hz, 2H).

EXAMPLE CCC12

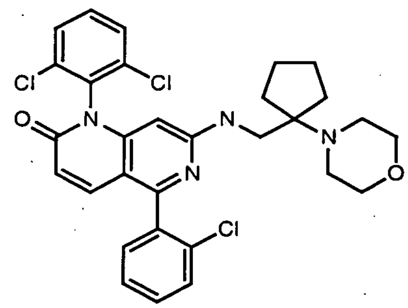
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40mg, 0.083mmol) (**COMPOUND HHH2**) and 1-(2-pyrrolidin-1-ylethyl)piperazine (77μL) in 0.5mL of DMSO was stirred under nitrogen at 130°C for 6.5h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (Waters Xterra C8 19x50 column, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 0:100 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 12min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 582.2 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 2.09 (m, 4H); 2.86 (brs, 4H); 3.02 (brs, 2H); 4.43 (m, 6H); 3.63 (brs, 4H).

EXAMPLE CCC13

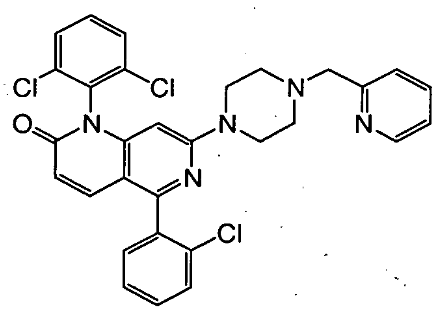
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[(1-morpholin-4-ylcyclopentyl)methyl]amino}-1,6-naphthyridin-2(1*H*)-one



A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40mg, 0.083mmol) (**COMPOUND HHH2**) and 1-(1-morpholin-4-ylcyclopentyl)methanamine (77μL) in 1mL of DMSO was stirred under nitrogen at 130°C for 12.35h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 583.2 (M+1). ^1H NMR (500 MHz, CD_3OD): selected peaks δ 1.84 (m, 9H); 3.34 (m, 1H); 3.49 (m, 5H); 3.80 (m. 4H).

EXAMPLE CCC14

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-1,6-naphthyridin-2(1*H*)-one

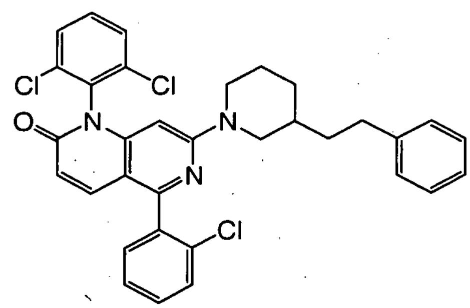


A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40mg, 0.083mmol) (**COMPOUND HHH2**), 1-(pyridin-2-ylmethyl)piperazine bis(trifluoroacetate) (170mg, 0.42mmol), and 1,8-

diazabicyclo[5.4.0]undec-7-ene (114µL, 0.75mmol) in 1mL of DMSO was stirred under nitrogen at 130°C for 3.6h. The mixture was cooled to rt, filtered, and purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 576.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 3.40 (t, J=5.1 Hz, 4H); 3.82 (brs, 4H); 4.50 (s, 2H).

EXAMPLE CCC15

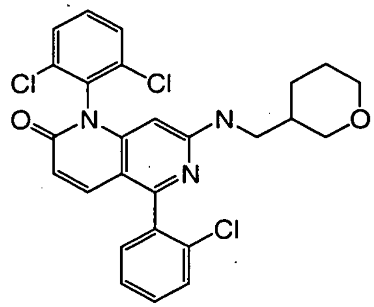
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[3-(2-phenylethyl)piperidin-1-yl]-1,6-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 3-(2-phenylethyl)piperidine hydrochloride by a procedure analogous to that described in **EXAMPLE CCC14**. Mass spectrum (ESI) 588.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.28 (m, 1H); 1.47 (m, 4H); 1.65 (m, 1H); 1.85 (d, J=11.5 Hz, 1H); 2.50 (m, 2H); 2.71 (m, 1H); 2.95 (m, 1H); 4.04 (m, 2H).

EXAMPLE CCC16

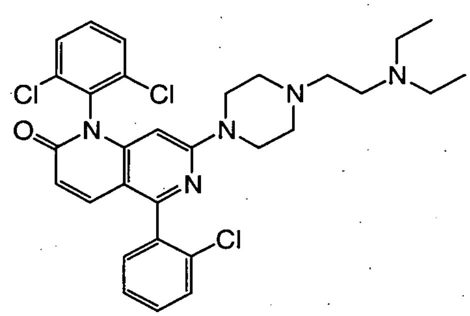
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(tetrahydro-2*H*-pyran-3-ylmethyl)amino]-1,6-naphthyridin-2(1*H*)-one



The title compound was prepared from 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (**COMPOUND HHH2**) and 1-tetrahydro-2*H*-pyran-3-ylmethanamine hydrochloride by a procedure analogous to that described in **EXAMPLE CCC14**. Mass spectrum (ESI) 514 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.25 (m, 1H); 1.52 (m, 4H); 1.81 (m, 1H); 3.23 (m, 1H); 3.37 (m, 2H); 3.46 (m, 1H); 3.86 (d, J=12.6 Hz, 1H).

EXAMPLE CCC17

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-[2-(diethylamino)ethyl]piperazin-1-yl}-1,6-naphthyridin-2(1*H*)-one

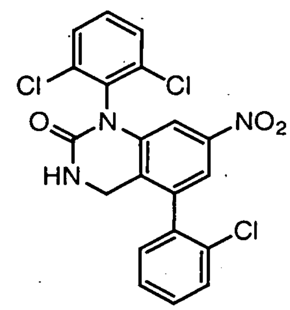


A mixture of 7-bromo-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (40mg, 0.083mmol) (**COMPOUND HHH2**) and *N,N*-diethyl-2-piperazin-1-ylethanamine (78μL) in 1mL of DMSO was stirred under nitrogen at 130°C for 3.6h and then stirred at rt for 2 days. The mixture was filtered and purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15min, at 20mL/min) to yield the title compound as the trifluoroacetate salt. Mass spectrum (ESI) 584.1 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.32 (t, J=7.1 Hz, 6H); 2.76

(t, J=4.8 Hz, 4H); 2.92 (t, J=6.2 Hz, 2H); 3.27 (m, 4H); 3.35 (t, J=6.2 Hz, 2H); 3.56 (t, J=4.6 Hz, 4H).

COMPOUND CCC3

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 1,3-dibromo-2-(bromomethyl)-5-nitrobenzene

To a mixture of 2,6-dibromo-4-nitrotoluene (5.00g, 16.95mmol) in CCl_4 (131mL) was added *N*-bromosuccinimide (4.22g, 23.73mmol) and dibenzoyl peroxide (411mg, 1.70mmol). The mixture was evacuated and flushed with argon three times, then heated using an oil bath. At reflux *azo-bis*-isobutyronitrile (278mg, 1.695mmol) was added. The reaction was stopped after 3.75h, cooled to rt and filtered washing with CCl_4. The filtrate was concentrated under reduced pressure to give a yellow solid, which was purified using flash chromatography on Biotage 40M column, eluting with 90:10 hexanes-CH_2Cl_2 to yield 1,3-dibromo-2-(bromomethyl)-5-nitrobenzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.8 (s, 2H), 8.4 (s, 2H).

STEP B: *N*-(2,6-dibromo-4-nitrobenzyl)-*N*-(4-methoxybenzyl)amine

4-methoxybenzylamine (2.15g, 15.7mmol) was added to a solution of 1,3-dibromo-2-(bromomethyl)-5-nitrobenzene (4.91g, 13.1mmol) in DMF (100mL) under nitrogen at rt. K_2CO_3 (1.99g, 14.4mmol) was then added and the reaction mixture was stirred at rt overnight. The reaction mixture was quenched with 500mL of water, and extracted with ethyl acetate (3 X 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography on Biotage 40M columns, eluting with 90:10 hexanes-ethyl acetate to provide *N*-(2,6-dibromo-4-nitrobenzyl)-*N*-(4-methoxybenzyl)amine as a red viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (d, J=3.6 Hz, 4H); 4.20 (s, 3H); 6.88 (d, J=8.4 Hz, 2H); 7.27 (d, J=5.9 Hz, 2H); 8.40 (s, 2H).

STEP C: <u>*N*-(2,6-dibromo-4-nitrobenzyl)-*N'*-(2,6-dichlorophenyl)-*N*-(4-methoxybenzyl)urea</u>

2,6-dichlorophenylisocyanate (1.54g, 8.18mmol) was added under nitrogen to a solution of *N*-(2,6-dibromo-4-nitrobenzyl)-*N*-(4-methoxybenzyl)amine (3.35g, 7.79mmol) in CH_2Cl_2 (95mL). The resulting mixture was stirred at rt for ca. 3h. The reaction mixture was then concentrated under reduced pressure to yield *N*-(2,6-dibromo-4-nitrobenzyl)-*N'*-(2,6-dichlorophenyl)-*N*-(4-methoxybenzyl)urea as a yellow solid. Mass spectrum (ESI) 616 (M+1).

STEP D: <u>5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one</u>

Diisopropylethylamine (1.78g, 13.8mmol) and CuI (2.63g, 13.8mmol) was added to *N*-(2,6-dibromo-4-nitrobenzyl)-*N'*-(2,6-dichlorophenyl)-*N*-(4-ethoxybenzyl)urea (4.25g, 6.88mmol) in DMF (150mL). After evacuating and flushing three times with argon, the reaction mixture was heated to 130°C for 3h, cooled to rt, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography on Biotage 40M columns, eluting with 80:20 hexanes-acetone to yield 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 536.0 (M+1).

STEP E: <u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7- nitro-3,4-dihydroquinazolin-2(1*H*)-one</u>

1.07g of 5-bromo-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one (1.99mmol) were dissolved in 26mL of toluene. Na_2CO_3 (1.26g, 11.9mmol), 2-chlorophenylboronic acid (934mg, 5.97mmol), and ethanol/water (6.4mL:6.4mL) were added under argon followed by $Pd(Ph_3P)_4$ (115 mg, 0.0995 mmol). The resulting reaction mixture was stirred at 100°C for ca.4h, cooled to rt, diluted with 150mL of ethyl acetate, washed with 2 x 100mL of saturated aqueous $NaHCO_3$ and 100mL of brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography on Biotage 40M column, eluting with 80:20 hexanes-acetone to yield 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7- nitro-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 568.1 (M+1).

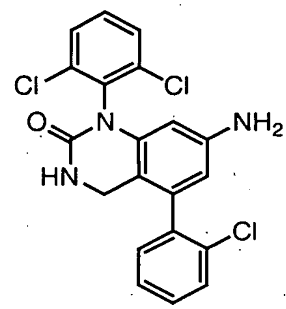
STEP F: <u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one</u>

A solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one (32mg, 0.56mmol) in 1mL trifluoroacetic acid was stirred at 95°C for 1.25h. The solvent was removed under

reduced pressure and the product was purified by preparative thin-layer chromatography, eluting with 93:7 CH_2Cl_2-methanol to yield 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 448 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.35 (½ ABq, J=15.5 Hz, 1H); 3.52 (½ ABq, J=15.5 Hz, 1H); 7.00 (s, 1H); 7.32 (d, J=2.1 Hz, 1H); 7.46 (m, 3H); 7.58 (m, 3H); 7.81 (s, 1H).

COMPOUND CCC4

7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

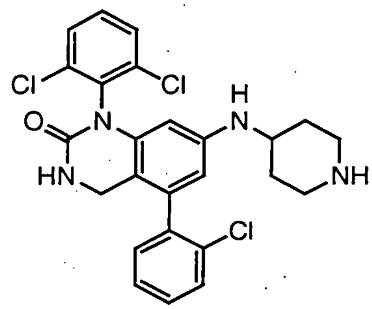
To a solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-nitro-3,4-dihydroquinazolin-2(1*H*)-one (20.0mg, 0.035mmol) in ethyl acetate (2mL) was added 10% Pd/C (14.5mg) under argon. Hydrogen was bubbled through and the reaction mixture was stirred under hydrogen for 1.5h. The reaction flask was purged with argon. The catalyst was filtered off washing with methanol. The filtrate was concentrated under reduced pressure to yield 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 538.2 (M+1).

STEP B: 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that on **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 418.0 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 4.07 (½ ABq, J=14.2 Hz, 1H); 4.18 (½ ABq, J=14.2 Hz, 1H); 5.54 (d, J=2 Hz, 1H); 6.24 (d, J=2.1 Hz, 1H); 7.29 (m, 1H); 7.40 (m, 2H); 7.47 (m, 2H); 7.58 (m, 2H).

EXAMPLE CCC18

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylamino)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]amino}piperidine-1-carboxylate

tert-butyl 4-oxopiperidine-1-carboxylate (37.9mg, 0.19mmol) was added to a mixture of 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (78mg, 0.15mmol) in 1mL of 1,2-dichloroethane. $NaBH(OAc)_3$ (58mg, 0.27mmol) was added after 45min. The reaction mixture was stirred at rt overnight. The reaction mixture was quenched with ca 5mL of 2.5M aqueous NaOH, extracted with (3 X 20mL) of ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by preparative thin-layer chromatography, eluting with 90:10 hexanes-ethyl acetate to yield *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]amino}piperidine-1-carboxylate. Mass spectrum (ESI) 721.2 (M+1).

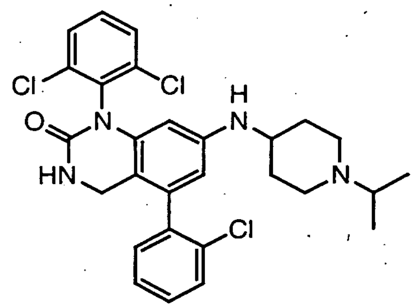
STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylamino)-3,4-dihydroquinazolin-2(1*H*)-one

The solution of *tert*-butyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]amino}piperidine-1-carboxylate (50mg, 0.069mmol) in 1mL of trifluoroacetic acid was heated at 95°C for 0.5h and then concentrated under reduced pressure. The product was purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15min, at 20Ml/min) to yield 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-

ylamino)-3,4-dihydroquinazolin-2(1*H*)-one as the trifluoroacetate salt, which was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give the free base. Mass spectrum (ESI) 501 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (m, 2H); 1.95 (m, 2H); 2.58 (m, 2H); 3.04 (d, J=12.3 Hz, 2H); 3.12 (m, 1H); 3.48 (brs, 1H); 4.12 (dd, J=13.5 Hz, J=2.18 Hz, 1H); 4.30 (dd, J=13.5 Hz, J=2.14 Hz, 1H); 4.98 (s, 1H); 5.34 (d, J=2.3 Hz, 1H); 6.12 (d, J=2.3 Hz, 1H); 7.31 (m, 4H); 7.49 (m, 3H).

EXAMPLE CCC19

<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(1-isopropylpiperidin-4-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one</u>

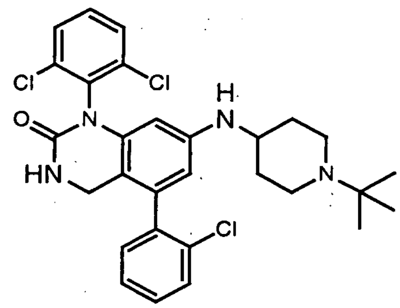


Acetone (98mg, 1.69mmol) was added to a mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(piperidin-4-ylamino)-3,4-dihydroquinazolin-2(1*H*)-one (85mg, 0.17mmol) in 2mL of 1,2-dichloroethane. 3 drops of acetic acid and $NaBH(OAc)_3$ (76mg, 0.34mmol) was then added. The reaction mixture was stirred under argon at rt over the weekend. The reaction mixture was quenched with 6mL of 2M aqueous NaOH and extracted with (3 X 10mL) of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by reverse-phase preparative HPLC (YMC C18 100x20mm, 90:10 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) to 10:90 water (0.1% trifluoroacetic acid)-CH_3CN (0.1% trifluoroacetic acid) over 15min, at 20mL/min.) The isolated trifluoroacetate salt was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to yield the title compound. Mass spectrum (ESI) 543.2 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (d, J=6.4 Hz, 6H); 1.40 (m, 2H); 1.97 (m, 2H); 2.18 (m, 2H); 2.72 (m, 1H); 2.82 (d, J=10.7 Hz, 2H); 3.06 (m, 1H); 3.49 (m, 1H); 4.15 (dd, J=13.5 Hz, J=1.6 Hz, 1H); 4.31 (dd, J=13.8 Hz, J=1.4

Hz, 1H); 5.01 (s, 1H); 5.36 (d, J=2 Hz, 1H); 6.13 (d, J=2.3 Hz, 1H); 7.35 (m, 4H); 7.50 (m, 3H).

EXAMPLE CCC20

7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

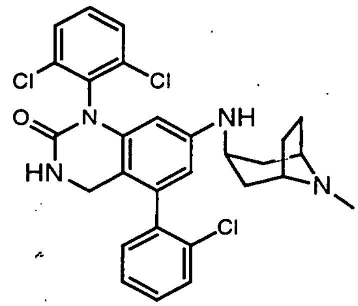
The 7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**COMPOUND CCC4, STEP A**) and the 1-*tert*-butylpiperidin-4-one (**COMPOUND PPA-1**) by a procedure analogous to that described in **EXAMPLE CCC18, STEP A**. Mass spectrum (ESI) 677.2 (M+1).

STEP B: 7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 7-[(1-*tert*-butylpiperidin-4-yl)amino]-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 557 (M+1). Trifluoroacetate salt: ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.08 (s, 9H); 1.41 (m, 2H); 1.98 (d, J=4.6 Hz, 2H); 2.17 (brs, 2H); 2.96 (d, J=8.7 Hz, 2H); 3.05 (brs, 1H); 4.13 (dd, J=1.8 Hz, J=13.7 Hz, 1H); 4.31 (dd, J=1.1 Hz, J=13.7 Hz, 1H); 5.17 (s, 1H).

EXAMPLE CCC21

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one

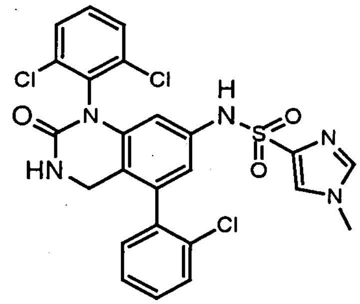
The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**COMPOUND CCC4, STEP A**) and 8-methyl-8-azabicyclo[3.2.1]octan-3-one by a procedure analogous to that described in **EXAMPLE CCC18, STEP A**. Mass spectrum (ESI) 661 (M+1).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 541 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.64 (d, J=14.5 Hz, 2H); 1.83 (d, J=12.1 Hz, 2H); 2.07 (m, 4H); 2.29 (s, 3H); 3.14 (brs, 2H); 3.36 (m, 1H); 3.81 (d, J=4.1 Hz, 1H); 4.14 (½ ABq, J=13.7 Hz, 1H); 4.32 (½ ABq, J=13.7 Hz, 1H).

COMPOUND CCC5

N-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methyl-1*H*-imidazole-4-sulfonamide



STEP A: N-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methyl-1*H*-imidazole-4-sulfonamide

To a solution of 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (150mg, 0.278mmol) (**COMPOUND CCC4, STEP A**) in 4mL of THF cooled to 0°C was added 1-methyl-1*H*-imidazole-4-sulfonyl chloride (100mg, 0.556mmol). A few crystals of 4-(dimethylamino)pyridine and diisopropylethylamine (53.9mg, 0.417mmol) were added. The resulting reaction mixture was stirred at 0°C for 20min, then heated to 70°C for ca. 7.5h. The reaction mixture was cooled to rt and partitioned between ethyl acetate and 1M aqueous HCl (added brine to improve the layer separation). The organic layer was concentrated under reduced pressure and triturated sequentially with Et_2O, methanol, and CH_2Cl_2 to yield the *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methyl-1*H*-imidazole-4-sulfonamide. Mass spectrum (ESI) 682.0 (M+1).

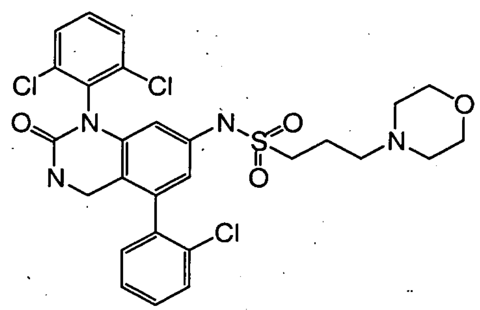
STEP B: N-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]- 1-methyl-1*H*-imidazole-4-sulfonamide

A solution of *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methyl-1*H*-imidazole-4-sulfonamide (114mg, 0.17mmol) in 1.5mL of trifluoroacetic acid was stirred at rt overnight. The resulting reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ followed by brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude solid was purified by preparatory thin-layer chromatography, eluting with 90:10 CH_2Cl_2-2M NH_3 in methanol to yield *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]- 1-methyl-1*H*-imidazole-4-sulfonamide. Mass spectrum (ESI) 562 (M+1). ^1H NMR (500 MHz, DMSO-d_6): δ 3.67 (s, 3H); 3.93 (½ ABq, J=14.9 Hz, 1H); 3.99 (½ ABq, J=14.9 Hz, 1H); 4.02 (s,

1H); 5.95 (d, J=2.1 Hz, 1H); 6.55 (d, J=1.9 Hz, 1H); 7.30 (m, 2H); 7.35 (s, 1H); 7.43 (m, 2H); 7.58 (m, 2H); 7.69 (s, 1H); 7.72 (d, J=8.2 Hz, 2H).

EXAMPLE CCC22

N-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide



STEP A: 3-chloro-*N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]propane-1-sulfonamide

The 3-chloro-*N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]propane-1-sulfonamide was prepared from 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**COMPOUND CCC4, STEP A**) and 3-chloropropane-1-sulfonyl chloride by a procedure analogous to that described in **COMPOUND CCC5, STEP A**. Mass spectrum (ESI) 678.1 (M+1).

STEP B: *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide

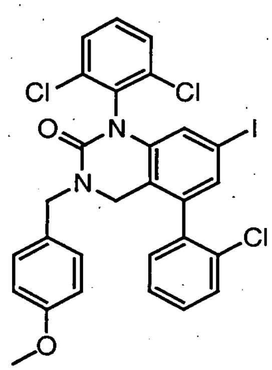
3-chloro-*N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]propane-1-sulfonamide (93mg, 0.14mmol) in morpholine (0.25mL) was heated at 130°C for 45min. The reaction mixture was cooled to rt, diluted with ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The product was purified by flash chromatography on a Biotage 40S column, eluting with 60:40 hexanes-acetone to yield *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide. Mass spectrum (ESI) 729 (M+1).

STEP C: *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide

The *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide was prepared from *N*-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-3-morpholin-4-ylpropane-1-sulfonamide by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 609 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.97 (m, 2H); 2.38 (m, 6H); 3.16 (t, J=6.9 Hz, 2H); 3.61 (t, J=4.6 Hz, 4H); 4.26 (dd, J=14.4 Hz, J=1.6 Hz, 1H); 4.38 (dd, J=14.4 Hz, J=1.6 Hz, 1H).

COMPOUND CCC6

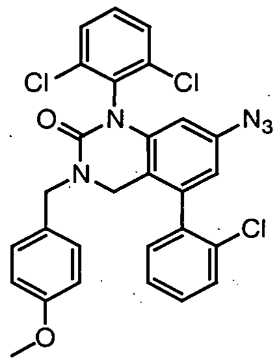
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodo-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one



To a mixture of 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (180.5mg, 0.335mmol) (**COMPOUND CCC4, STEP A**) in 2mL of CH_2I_2 was added *tert*-butylnitrite (57.7mg, 0.503mmol). The reaction mixture was heated at 90°C for ca. 45min, cooled to rt, and purified by flash chromatography on a Biotage 40M column, eluting with hexanes followed by 2:1 hexanes-acetone to yield the title compound. Mass spectrum (ESI) 649.0 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H); 3.99 (½ ABq, J=15.1 Hz, 1H); 4.14 (½ ABq, J=14.8 Hz, 1H); 4.39 (½ ABq, J=14.9 Hz, 1H); 4.63 (½ ABq, J=14.8 Hz, 1H); 6.43 (d, J=1.4 Hz, 1H); 6.80 (m, 2H); 7.10 (dd, J=7.6 Hz, J=1.6 Hz, 1H); 7.15 (d, J=8.6 Hz, 2H); 7.19 (d, J=1.6 Hz, 1H); 7.26 (m, 1H); 7.33 (m, 1H); 7.37 (t, J=8.2, 1H); 7.43 (m, 1H); 7.53 (m, 2H).

COMPOUND CCC7

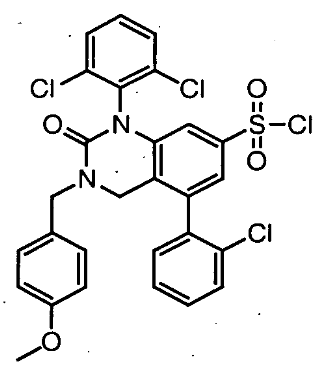
7-azido-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one



To a mixture of 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (20mg, 0.037mmol) **(COMPOUND CCC4, STEP A)** in 0.9mL of acetic acid at 0°C was added $NaNO_2$ (2.6mg dissolved in 79μL of water). The reaction mixture was stirred at this temperature for 1h. NaN_3 (3.6mg dissolved in 79μL of water) was then added and the reaction mixture was stirred at 0°C for another 0.25h. The reaction mixture was diluted with ca.5mL of ethyl acetate, washed with 1M aqueous NaOH, dried (Na_2SO_4), and concentrated under reduced pressure to yield the title compound. Mass spectrum (ESI) 564.1 (M+1).

COMPOUND CCC8

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride

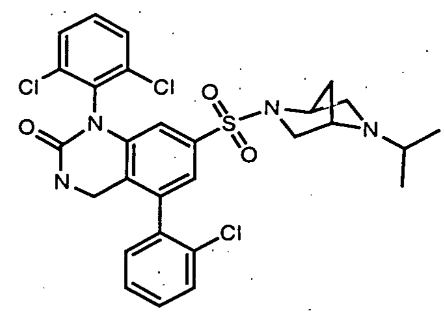


A mixture of 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (300mg, 0.557mmol)

(**COMPOUND CCC4, STEP A**), concentrated HCl (2.2mL), and acetic acid (0.6mL) was cooled to ca. –10°C. A solution of $NaNO_2$ (57.7mg, 0.836mmol) in 0.9mL of water was added and the reaction mixture was stirred at –10°C for 0.5h. To the reaction mixture was added a slurry of $CuCl_2$ (57.9mg, 0.418mmol) in acetic acid (1.3mL) (through which SO_2 had been bubbled for 0.25h), and the temperature of the reaction mixture was kept at ca. –10°C for 1h after the addition, while SO_2 was bubbled through the reaction mixture for 0.5h after the addition. The reaction mixture was then stirred at rt overnight. Added the mixture to 25mL of ice/water and extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The product was purified by preparative thin-layer chromatography, eluting with 50:50 hexanes-acetone to yield the titled compound.

EXAMPLE CCC23

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

2-isopropyl-2,5-diazabicyclo[2.2.1]heptane (**INTERMEDIATE ABA2**) (35 μL, ca. 0.249mmol) and diisopropylethylamine (32mg, 0.249mmol) were added to a mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (103mg, 0.166mmol) (**COMPOUND CCC8**) in 2mL THF at 0°C. The mixture was warmed to rt, stirred at this temperature for 0.5h, and concentrated under reduced pressure. The residue was diluted with ethyl acetate and added to 6mL of 1M aqueous HCl. The phases were separated and the aqueous was extracted with 3 x 15mL of ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and

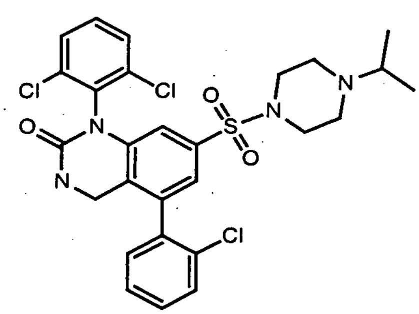
concentrated under reduced pressure. The product was purified by preparative thin-layer chromatography, eluting with 93:7 CH_2Cl_2-methanol to yield the 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 725 (M+1).

STEP B: <u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one</u>

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(5-isopropyl-2,5-diazabicyclo[2.2.1]hept-2-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 605 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$):selected peaks δ 1.01 (d, J=5.9 Hz, 6H); 1.12 (m, 1H); 1.69 (d, J=9.8 Hz, 1H); 2.51 (t, J=8.9 Hz, 1H); 2.56 (m, 1H), 2.93 (m, 1H); 3.02 (d, J=9.6 Hz, 1H); 3.49 (d, J=9.9 Hz, 1H); 3.62 (s, 1H); 4.09 (d, J=39.1, 1H); 4.37 (½ ABq, J=15.4 Hz, 1H); 4.45 (½ ABq, J=15.4 Hz, 1H).

EXAMPLE CCC24

<u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one</u>



STEP A: <u>5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one</u>

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride

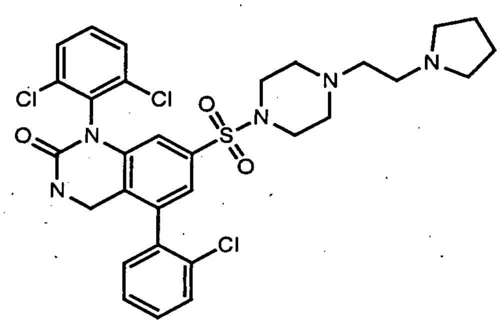
(**COMPOUND CCC8**) and 1-isopropylpiperazine by a procedure analogous to that described in **EXAMPLE CCC23, STEP A**. Mass spectrum (ESI) 713 (M+1).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)sulfonyl]-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 593 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$):selected peaks δ 1.03 (d, J=6.6 Hz, 6H); 2.57 (t, J=5Hz, 4H); 2.69 (m, 1H); 3.00 (brs, 4H); 4.34 (dd, J=15.3 Hz, J=1.6 Hz, 1H); 4.46 (dd, J=15.3 Hz, J=1.6 Hz, 1H).

EXAMPLE CCC25

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride

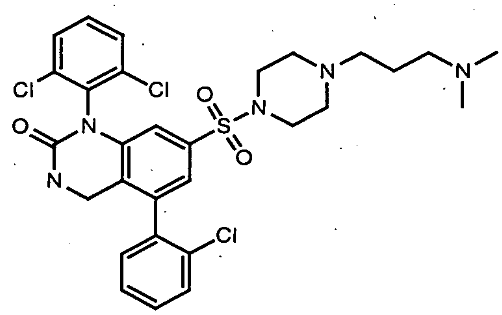
The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride was prepared from 7-amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (**COMPOUND CCC4**) by a procedure analogous to that described in **COMPOUND CCC8**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (½ ABq, J=16.0 Hz, 1H); 4.47 (½ ABq, J=16.0 Hz, 1H); 6.70 (d, J=1.8 Hz, 1H); 7.30 (dd, J=7.1 Hz, J=2.0 Hz, 2H); 7.41 (m, 3H); 7.54 (m, 3H).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride and 1-(2-pyrrolidin-1-ylethyl)piperazine by a procedure analogous to that described in **EXAMPLE CCC23, STEP A**, except that no diisopropylethylamine was used. Mass spectrum (ESI) 648 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.81 (brs, 4H); 2.58 (m, 12H); 3.00 (brs, 4H); 4.35 (dd, J=15.4 Hz, J=1.6 Hz, 1H); 4.46 (dd, J=15.4 Hz, J=1.6 Hz, 1H).

EXAMPLE CCC26

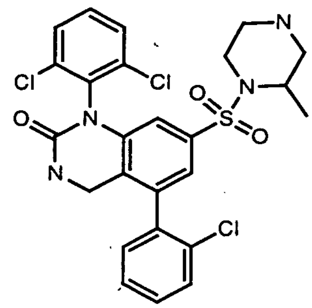
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[3-(dimethylamino)propyl]piperazin-1-yl}sulfonyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (**EXAMPLE CCC25, STEP A**) *N,N*-dimethyl-3-piperazin-1-ylpropan-1-amine by a procedure analogous to that described in **EXAMPLE CCC25, STEP B**. Mass spectrum (ESI) 636 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 2.22 (s, 6H); 2.27 (t, J=7.3 Hz, 2H); 2.37 (t, J=7.3 Hz, 2H); 2.49 (brs, 4H); 3.00 (brs, 4H); 4.36 (½ ABq, J=15.3 Hz, 1H); 4.46 (½ ABq, J=15.3 Hz, 1H).

EXAMPLE CCC27

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one

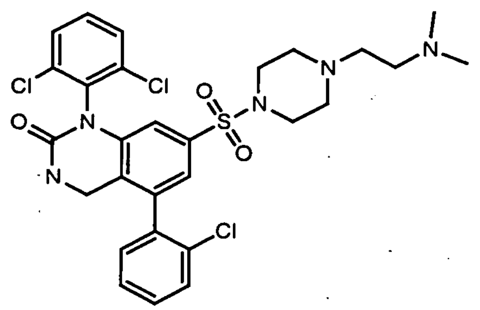
The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (**COMPOUND CCC8**) and *tert*-butyl 3-methylpiperazine-1-carboxylate by a procedure analogous to that described in **EXAMPLE CCC25, STEP B**. Mass spectrum (ESI) 729 (M - *t*-Bu + 1).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(2-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3, STEP F**. Mass spectrum (ESI) 565 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.11 (m, 3H); 2.64 (m, 2H); 2.83 (m, 2H); 3.07 (m, 1H); 3.43 (m, 1H); 3.91 (m, 1H); 4.35 (½ ABq, J=15.3 Hz, 1H); 4.45 (½ ABq, J=15.3 Hz, 1H).

EXAMPLE CCC28

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

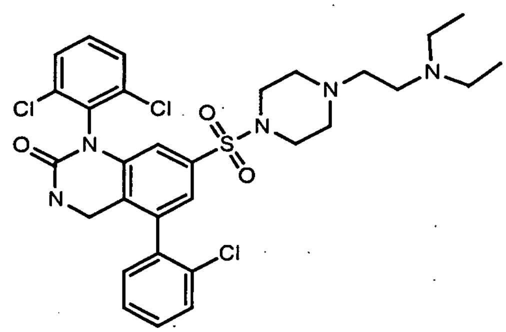
The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (**COMPOUND CCC8**) and *N*,*N*-dimethyl-2-piperazin-1-ylethanamine by a procedure analogous to that described in **EXAMPLE CCC25**, **STEP B**. Mass spectrum (ESI) 742 (M+1).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}sulfonyl)-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **COMPOUND CCC3**, **STEP F**. Mass spectrum (ESI) 622 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 2.23 (s, 6H); 2.39 (t, J=6.4 Hz, 2H); 2.50 (t, J=6.6 Hz, 2H); 2.53 (m, 4H); 3.01 (brs, 4H); 4.34 (½ ABq, J=15.3 Hz, 1H); 4.46 (½ ABq, J=15.3 Hz, 1H).

EXAMPLE CCC29

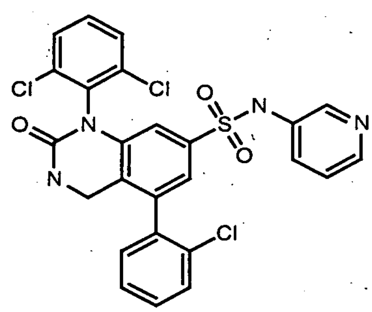
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-({4-[2-(diethylamino)ethyl]piperazin-1-yl}sulfonyl)-3,4-dihydroquinazolin-2(1*H*)-one



The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (**EXAMPLE CCC25, STEP A**) and *N,N*-diethyl-2-piperazin-1-ylethanamine by a procedure analogous to that described in **EXAMPLE CCC25, STEP B**. Mass spectrum (ESI) 650 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): selected peaks δ 1.03 (t, J=7.1 Hz, 6H); 2.51 (m, 12H); 3.00 (brs, 4H); 4.35 (dd, J=15.4 Hz, J=1.6 Hz, 1H); 4.46 (½ ABq, J=15.4 Hz, J=1.6 Hz, 1H).

COMPOUND CCC9

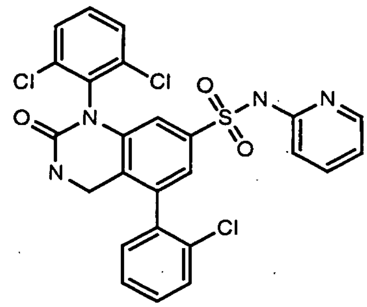
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-*N*-pyridin-3-yl-1,2,3,4-tetrahydroquinazoline-7-sulfonamide



Pyridin-3-amine (9.4mg, 0.10mmol) and pyridine (6μL, 0.075mmol) were added to a mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (25mg, 0.050mmol) (**EXAMPLE CCC25, STEP A**) in 0.5mL THF. The mixture was stirred at rt overnight, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-NH_3 in methanol to yield the title compound. Mass spectrum (ESI) 559 (M+1).

COMPOUND CCC10

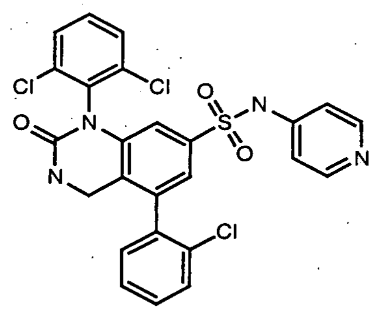
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-*N*-pyridin-2-yl-1,2,3,4-tetrahydroquinazoline-7-sulfonamide



Pyridin-2-amine (14mg, 0.15mmol) and pyridine (12μL, 0.15mmol) were added to a mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (25mg, 0.050mmol) (**EXAMPLE CCC25, STEP A**) in 0.5mL THF. The mixture was stirred at rt overnight, then heated for 3h at 70°C, and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 95:5 CH_2Cl_2-NH_3 in methanol to yield the title compound. Mass spectrum (ESI) 559.0 (M+1).

COMPOUND CCC11

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-*N*-pyridin-4-yl-1,2,3,4-tetrahydroquinazoline-7-sulfonamide

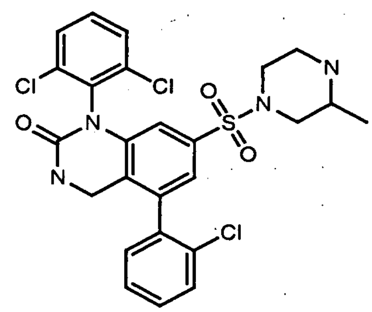


The title compound was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (**EXAMPLE CCC25, STEP A**) and pyridin-4-amine by a procedure analogous to that described in **COMPOUND CCC10, STEP A**. Mass spectrum (ESI) 559 (M+1). ^{1}H NMR (500 MHz, CD_3OD): δ 4.30 (ABq, J=23.3 Hz, J=6.0 Hz, 2H); 6.57 (d, J=1.6

Hz, 1H); 7.29 (brs, 2H); 7.40 (m, 1H); 7.48 (m, 3H); 7.57 (m, 2H); 7.65 (d, J=8.1 Hz, 2H); 8.31 (brs, 2H).

EXAMPLE CCC30

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one



STEP A: benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]sulfonyl}-2-methylpiperazine-1-carboxylate

Benzyl 2-methylpiperazine-1-carboxylate (34mg, 0.144mmol) and diisopropylethylamine (19mg, 0.144mmol) were added to a mixture of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-sulfonyl chloride (60mg, 0.096mmol) (**COMPOUND CCC8**) in 1mL THF. The mixture was heated to 80°C and stirred at this temperature for ca. 1h. The reaction mixture was cooled to rt and concentrated. The residue was purified by preparative thin-layer chromatography, eluting with 50:50 hexanes-acetone to yield benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]sulfonyl}-2-methylpiperazine-1-carboxylate. Mass spectrum (ESI) 819.1 (M+1).

STEP B: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one

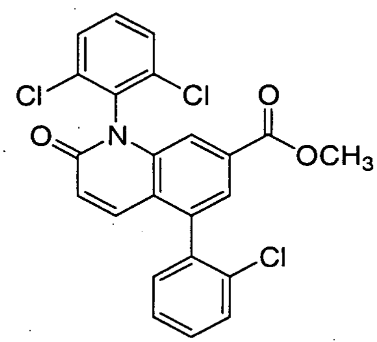
The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from benzyl 4-{[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]sulfonyl}-2-methylpiperazine-1-carboxylate by a procedure analogous to that described in **COMPOUND CCC4, STEP A**.

STEP C: 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one

The 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one was prepared from 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3-(4-methoxybenzyl)-7-[(3-methylpiperazin-1-yl)sulfonyl]-3,4-dihydroquinazolin-2(1*H*)-one by a procedure analogous to that described in **EXAMPLE CCC18, STEP B**. Mass spectrum (ESI) 565 (M+1). ^{1}H NMR (500 MHz, CD_3OD): selected peaks δ 1.29 (m, 3H); 2.43 (t, J=10.9, 1H); 2.65 (m, 1H); 3.19 (m, 1H); 3.43 (m, 2H); 3.72 (m, 2H); 4.32 (dd, J=16.0 Hz, J=7.1 Hz, 1H); 4.40 (dd, J=16.0 Hz, J=7.1 Hz, 1H).

COMPOUND CCA1

Methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxylate



STEP A: Methyl 3,5-dibromo-4-formylbenzoate

Methyl 3,5-dibromo-4-(bromomethyl)benzoate (**INTERMEDIATE 24**) (3.9g) was dissolved in acetonitrile (100mL) and to this was added 4Å molecular sieves and N-methylmorpholine N-oxide (1.18g) and the reaction heated to 50°C for 12h. The reaction mixture was poured into brine and extracted into ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluting with 90% hexane:10% ethyl acetate to give the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 10.27 (s, 1H); 8.29 (s, 2H); 3.99 (s, 3H).

STEP B: *tert*-Butyl (diphenoxyphosphoryl)acetate

To a solution of diphenylphosphite (2.25mL) in dichloromethane at 0°C was added t-butylbromoacetate (1.48mL) followed by triethylamine (1.95mL). The mixture was stirred at 0°C for 15min and then at rt for 1h before being quenched with water and extracted into ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate to

give the title compound. ^1H NMR (500MHz, $CDCl_3$): δ 7.40-7.18 (m, 10H); 3.22 (s, 1H); 3.18 (s, 1H); 1.50 (s, 9H).

STEP C: Methyl 3,5-dibromo-4-[(1*Z*)-3-*tert*-butoxy-3-oxoprop-1-enyl]benzoate

To a solution of *tert*-butyl (diphenoxyphosphoryl)acetate (267mg) in THF (7.5mL) at 0°C under nitrogen was added sodium hydride and the mixture stirred for 15min until gas evolution ceased. This anion mixture was then cooled to –78°C and a solution of methyl 3,5-dibromo-4-formylbenzoate (262mg) in THF (7.5mL) was added dropwise. The reaction mixture was stirred at –78°C for an additional 40min before being quenched with saturated ammonium chloride solution, extracted into ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluting with 90% hexane:10% ethyl acetate to give the title compound which also contained 20% of the E double-bond isomer. No attempt was made to separate these isomers at this stage. ^1H NMR (500MHz, $CDCl_3$): δ 8.23 (s, 1H, E isomer); 8.21 (s, 1H, Z isomer); 7.57 (d, J=16.3Hz, 1H, E isomer); 6.76 (d, J=11.9Hz, 1H, Z isomer); 6.38 (d, J=16.3Hz, 1H E isomer); 6.12 (d, J=11.9Hz, 1H Z isomer); 3.954 (s, 3H, E isomer); 3.948 (s, 3H, Z isomer); 1.28 (s, 9H, both isomers). Mass spectrum: m/z 365 (M+H-t-Bu).

STEP D: (2*Z*)-3-[2,6-Dibromo-4-(methoxycarbonyl)phenyl]prop-2-enoic acid

To a solution of the methyl 3,5-dibromo-4-[(1*Z*)-3-*tert*-butoxy-3-oxoprop-1-enyl]benzoate (340mg) (contaminated with 20% of the E isomer from the previous step) in dichloromethane (1mL) was added trifluoroacetic acid (10mL) and the reaction stirred at ambient temperature for 45min. After this time the reaction mixture was concentrated, toluene (100mL) added and then concentrated again. The crude product was concentrated from toluene several more times to ensure the removal of all of the trifluoroacetic acid ultimately yielding the title compound (contaminated with 20% of the E isomer) which required no further purification. ^1H NMR (500MHz, $CDCl_3$): δ 10.19 (br.s. 1H, both isomers); 8.24 (s, 1H, E isomer); 8.20 (s, 1H, Z isomer); 7.74 (d, J=16.3Hz, 1H, E isomer); 6.98 (d, J=11.9Hz, 1H, Z isomer); 6.45 (d, J=16.3Hz, 1H E isomer); 6.24 (d, J=11.9Hz, 1H Z isomer); 3.95 (s, 3H, both isomers). Mass spectrum: m/z 365 (M+H-t-Bu).

STEP E: Methyl 3,5-dibromo-4-{(1*Z*)-3-[(2,6-dichlorophenyl)amino]-3-oxoprop-1-enyl}benzoate

To a solution of (2*Z*)-3-[2,6-dibromo-4-(methoxycarbonyl)phenyl]prop-2-enoic acid (1.24g) (contaminated with 20% of the E isomer) in dichloromethane (34mL) at 0°C under nitrogen atmosphere was added oxalyl bromide (2mL of a 2M solution in dichloromethane) followed by

dimethylformamide (170μL). The mixture was then warmed to rt and stirred until all gas evolution had ceased. The reaction was cooled again to 0°C where diisopropylethylamine (831μL) and 2,6-dichloroaniline (607mg) were added and the reaction warmed to rt and stirred for 16h. The reaction mixture was then poured into brine and extracted into ethyl acetate. A small amount of unreacted starting acid was removed by washing the organic layer with saturated sodium bicarbonate solution, before drying over $MgSO_4$ and concentrating. The residue was purified by column chromatography on silica gel to give the title compound still contaminated with 20% of the E isomer. ^{1}H NMR (500MHz, $CDCl_3$): δ 8.99 (br.s, 1H, Z isomer); 8.26 (br.s, 1H, E isomer); 8.20 (s, 1H, Z isomer); 7.80-6.40 (m, 6H); 3.96 (s, 3H, E isomer); 3.92 (s, 3H, Z isomer). Mass spectrum: m/z 507 (M+H).

STEP F: Methyl 5-bromo-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxylate

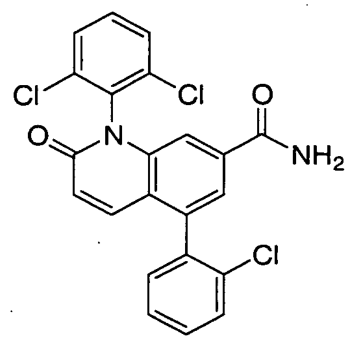
Methyl 3,5-dibromo-4-{(1Z)-3-[(2,6-dichlorophenyl)amino]-3-oxoprop-1-enyl}benzoate (1.25g)(contaminated with 20% of the E isomer) was dissolved in dimethylformamide(36mL) and the solution degassed with argon. Copper (I) iodide (340mg) and dry potassium carbonate (468mg) were added and the mixture heated to 80°C for 30min. The reaction mixture was poured into 5% ammonium hydroxide solution and extracted into ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluting with 80% hexane : 20% ethyl acetate to give the title compound.
^{1}H NMR (500MHz, $CDCl_3$): δ 8.31 (d, J=9.8Hz, 1H); 8.15 (s, 1H); 7.60 (d, J=8.0Hz,1H); 7.50 (t, J=8Hz, 2H); 7.12 (s, 1H); 6.98 (d, J=10.1Hz, 1H); 3.90 (s, 3H). Mass spectrum: m/z 428 (M+H).

STEP G: Methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxylate

Methyl 5-bromo-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxylate (80mg), 2-chlorophenylboronic acid (58mg), palladium tetrakis(triphenylphosphine) (22mg) and 1M aqueous sodium carbonate (450μL) were mixed in ethylene glycol dimethyl ether (2mL), degassed with argon and then heated to reflux for 90min. The cooled reaction mixture was diluted with ether, filtered through celite and concentrated. The residue was purified by silica gel chromatography eluting with 70% hexane:30% ethyl acetate to give the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.82 (d, J=1.4Hz, 1H); 7.65-7.39 (m, 8H); 7.23 (s, 1H); 6.82 (d, J=9.9Hz, 1H), 3.90 (s, 3H). Mass spectrum: m/z 458 (M+H).

COMPOUND CCA2

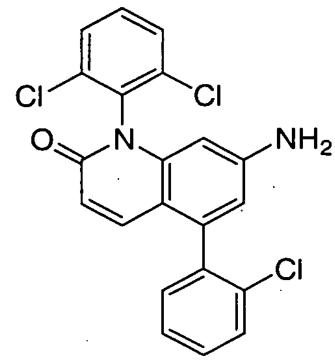
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxamide



A solution of methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxylate (1.28g) in methanol (100mL) was treated with 1M potassium hydroxide (40mL) and the reaction stirred at rt for 3h. The reaction mixture was then acidified with 1N hydrochloric acid (100mL) and extracted into dichloromethane. The organic phase was dried over $MgSO_4$, concentrated and the residue was dissolved in THF (16mL). 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (314mg) and 1-hydroxybenzotriazole hydrate (251mg) were then added and this mixture was stirred at rt for 45min before the addition of concentrated ammonium hydroxide (111μL). The reaction was then stirred at rt for a further 24h before being concentrated and purified by silica gel chromatography eluting with hexane/acetone to give the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.65-7.39 (m, 9H); 7.08 (s, 1H); 6.80 (d, J=9.9Hz, 1H); 6.02 (br.s, 1H); 5.70 (br.s, 1H). Mass spectrum: m/z 443 (M+H).

COMPOUND CCA3

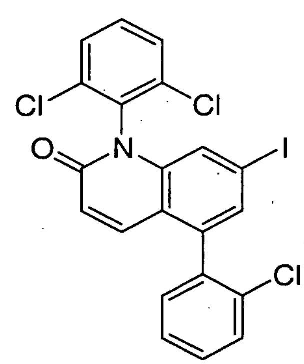
7-Amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one



To 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2-dihydroquinoline-7-carboxamide (920mg) in dioxane (330mL) was added 5N NaOH (10mL) and water (41mL) followed by sodium hypochlorite (19.3mL of a 10-13% aqueous solution) and the reaction mixture heated to 60°C for 2h. The cooled reaction mixture was then poured into brine and extracted into ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate to give the title compound. ^1H NMR (500MHz, $CDCl_3$): δ 7.61-7.32 (m, 8H); 6.48 (d, J=2.1Hz, 1H); 6.45 (d, J=9.7Hz, 1H); 5.73 (d, J=2.1Hz, 1H); 4.00 (br.s, 2H). Mass spectrum: m/z 415 (M+H).

COMPOUND CCA4

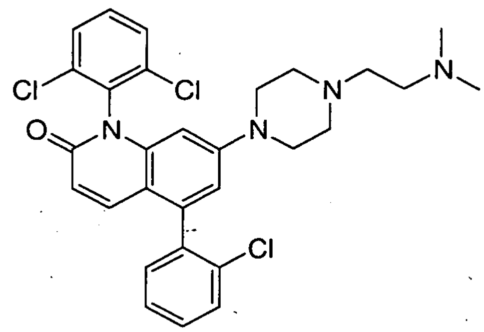
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one



7-Amino-5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)quinolin-2(1*H*)-one (560mg), diiodomethane (3.5mL) and t-butylnitrite (238μl of a 90% solution) were heated to 90°C for 15min. The reaction mixture was directly loaded onto a silica gel column, with no work-up, and eluted with hexane/ethyl acetate to give the title compound. ^1H NMR (500MHz, $CDCl_3$): δ 7.65-7.37 (m, 9H); 6.89 (s, 1H); 6.74 (d, J=10.0Hz, 1H). Mass spectrum: m/z 528 (M+H).

EXAMPLE CCA1

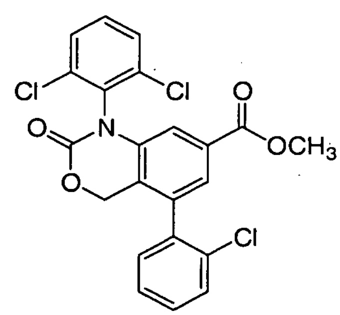
5-(2-Chlorophenyl)-1-(2,6-dichlorophenyl)-7-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}quinolin-2(1*H*)-one



To the 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-iodoquinolin-2(1*H*)-one (48mg) in an oven-dried flask was added 18-crown-6 (34mg), sodium t-butoxide (13mg), tris(dibenzylideneacetone)dipalladium (0) (8.3mg) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (17mg) and the flask carefully filled with argon. The *N,N*-dimethyl-*N*-(2-piperazin-1-ylethyl)amine (17mg) and THF (2mL) were then added and the reaction stirred at rt for 16h. The reaction mixture was then filtered and concentrated and the residue purified by reverse phase HPLC to yield the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.62-7.35 (m, 8H); 6.74 (d, J=2.3Hz, 1H); 6.49 (d, J=9.8Hz, 1H); 5.86 (d, J=2.1Hz, 1H); 3.16 (t, J=4.8Hz, 4H); 2.57 (t, J=5.1Hz, 4H); 2.53-2.46 (m, 4H), 2.28 (s, 6H). Mass spectrum: m/z 557 (M+H).

COMPOUND DDD-1

Methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate



Step A: methyl 3,5-dibromo-4-(hydroxymethyl)benzoate

To a stirred solution of methyl 3,5-dibromo-4-(bromomethyl)benzoate **(INTERMEDIATE 24)** (12.53g, 32.4mmol, 1eq) in dioxane (100mL) and water (100mL) was added $CaCO3$ (8.1g, 81mmol, 2.5eq). The mixture was warmed to and stirred at 100°C until reaction was complete by HPLC analysis. The mixture was cooled and the solvent removed under reduced pressure. The residue was diluted with water and extracted 3x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated giving methyl 3,5-dibromo-4-(hydroxymethyl)benzoate. The material was taken immediately to the next step.

Step B: methyl 3,5-dibromo-4-[({[(2,6-dichlorophenyl)amino]carbonyl}oxy)methyl]benzoate

To a stirred solution of methyl 3,5-dibromo-4-(hydroxymethyl)benzoate (11g, 34mmol, 1eq) in CH_2Cl_2 (50mL) was added 2,6-dichlorophenylisocyanate (7g, 37.2mmol, 1.1eq) and 4-N,N-dimethylaminopyridine (few crystals). Stirred at rt. After 15min, the flask was thick with precipitate. Added 50mL CH_2Cl_2 to facilitate stirring and let stir overnight. Removed the CH_2Cl_2 under reduced pressure. Triturated the residue with Et_2O and collected the solids giving methyl 3,5-dibromo-4-[({[(2,6-dichlorophenyl)amino]carbonyl}oxy)methyl]benzoate. ^1H NMR (500 MHz, $CDCl_3$): $\delta CHCl_3$ 8.23 (sH, s); 7.38 (2H, d, J=8Hz); 7.19 (1H, t, J=8 Hz); 6.39 (1H br s); 5.58 (2H, s); 3.96 (3H, s).

Step C: methyl 5-bromo-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate

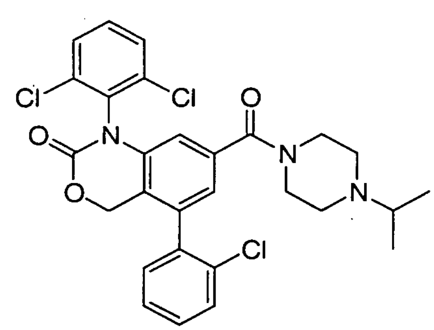
To a solution of methyl 3,5-dibromo-4-[({[(2,6-dichlorophenyl)amino]carbonyl}oxy)methyl]benzoate (1g, 1.96 mmol, 1 eq) in DMF (20mL) was added CuI (411mg, 2.16mmol, 1.1eq) and diisopropylethylamine (0.51mL, 2.95mmol, 1.5eq). Degassed the reaction flask with argon and placed in a 140°C oil bath. After 2.5h the reaction was cooled. The mixture was filtered to remove inorganics. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and washed with water. The aqueous layer was back-extracted 2x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was triturated with Et_2O leaving 283mg of solid methyl 5-bromo-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate. The supernatant was further purified by flash column chromatography on silica gel eluting with 2:1 CH_2Cl_2/hexanes giving an additional 309mg of not quite pure product. Mass spectrum (ESI) 430.0 (M+1); 432.0 (M+3), 434.0 (M+5).

Step D: methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate

A stirred solution of methyl 5-bromo-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate (280mg, 0.65mmol, 1eq) in toluene (9mL) was degassed with argon. To this solution was added 2-chlorophenylboronic acid (305mg, 1.95mmol, 3eq) and Na_2CO_3 (427mg, 4.03mmol, 6.2eq). The mixture was again degassed with argon. To the stirred mixture was then added water (2mL) and ethanol (2mL). The mixture was degassed with argon. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (37mg, 0.032mmol, 0.05eq). The reaction vessel was placed in a 100°C oil bath and stirred under argon. After 1.5h HPLC analysis indicated partial conversion of starting material. Added small amount tetrakis(triphenylphosphine)palladium(0) and continued to stir. After additional 1h at 100°C HPLC analysis showed little change. The mixture was cooled, diluted with ethyl acetate, washed 2x with saturated aqueous $NaHCO_3$, and 1x with brine, The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography eluting with 6:1 hexanes/ ethyl acetate giving 193mg methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate.
Mass spectrum (ESI) 462 (M+1); 464 (M+3).

EXAMPLE DDD1

5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)carbonyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one

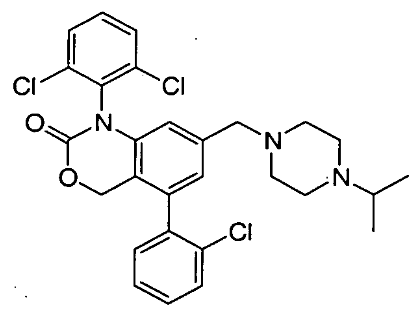


To a dry flask charged with anhydrous CH_2Cl_2 (1mL) was added 1-isopropylpiperazine (0.057mL, 0.434mmol, 2eq). The mixture was cooled to 0°C under nitrogen. To this cooled mixture was added $Al(CH_3)_3$ (0.217mL of a 2M toluene solution, 0.434mmol, 2eq). After 15min, methyl 5-(2-chlorophenyl)-1-(2,6-

dichlorophenyl)-2-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-7-carboxylate (100mg, 0.217mmol, 1eq) was dissolved in CH_2Cl_2 (1mL) and added to the aluminum reagent at 0°C under nitrogen. After 2min the cooling bath was removed. Let stir at rt for 5d. The reaction was diluted with CH_2Cl_2, and washed with water. The aqueous layer was back extracted 2x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography on silica gel eluting with 2:1 hexanes/acetone giving 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)carbonyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one. Mass spectrum (ESI) 458.0 (M+1); 460 (M+3).

EXAMPLE DDD2

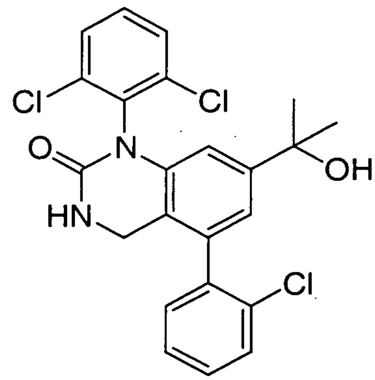
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)methyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one



To a stirred solution of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)carbonyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (31mg, 0.055mmol, 1eq) in THF (0.1mL) at 0°C under nitrogen was added a solution of borane in THF (0.1mL of a 1M solution, 0.1mmol, 1.8eq). The mixture was stirred 5min at 0°C and then the cooling bath was removed. The mixture was brought to and maintained at reflux for 2h (twice added 0.1mL of THF due to solvent loss). The mixture was cooled. To the reaction was added 6N aqueous HCl (0.1mL) and the mixture was heated in a 70°C oil bath for 15min. The mixture was cooled and diluted with CH_2Cl_2 and aqueous $NaHCO_3$. Aqueous 2N NaOH was added to increase basicity. Mixed and separated the layers. The aqueous layer was back extracted 2x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography on silica gel giving 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-[(4-isopropylpiperazin-1-yl)methyl]-1,4-dihydro-2*H*-3,1-benzoxazin-2-one. Mass spectrum (ESI) 544.2 (M+1); 546.2 (M+3).

COMPOUND DDD-2

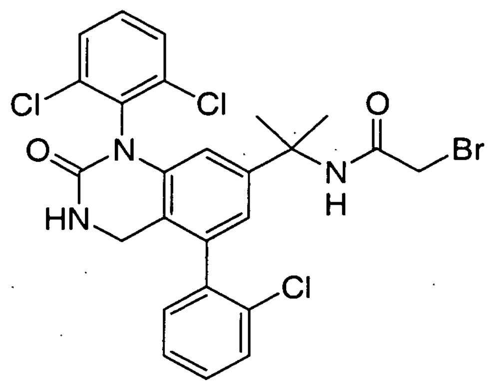
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-hydroxy-1-methylethyl)-3,4-dihydroquinazolin-2(1*H*)-one



To a stirred solution of methyl 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (1g, 2.17mmol, 1eq) in THF (20mL) under nitrogen at 0°C was added a solution of methylmagnesium bromide (4.66mL of a 1.4M solution in toluene, 6.52mmol, 3eq). The cooling bath was removed and the mixture allowed to stir 2h and then the reaction was brought to and maintained at reflux for 1h. The mixture was cooled and additional methylmagnesium bromide (2mL of 1.4M solution in toluene) was added. A large amount of precipitate formed. Let stir 1h. HPLC analysis showed some starting material still present. Added methylmagnesium bromide (2mL of 1.4M solution in toluene) and let stir overnight. Poured the reaction into a separatory funnel containing water. Made acidic by addition of 2N aqueous HCl. Extracted 3x with CH_2Cl_2. Combined the organic extracts, dried over anhydrous Na_2SO_4, filtered and concentrated giving 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-hydroxy-1-methylethyl)-3,4-dihydroquinazolin-2(1*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta CHCl_3$ 7.54-7.50 (3H, m); 7.40-7.31 (4H, m); 6.98 (1H, d, J = 1.6 hz); 6.35 (1H, d, J = 1.6 Hz); 5.21 (1H, br s); 4.43 (1H, dd, J = 14.4 Hz, J = 1.6 Hz); 4.26 (1H, dd, J = 114.4 Hz, J = 1.8 Hz); 1.47 (3H s); 1.46 (3H, s).

COMPOUND DDD-3

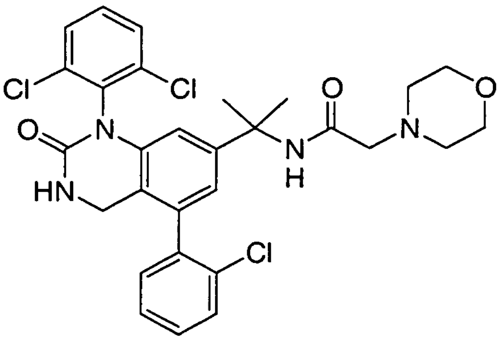
2-bromo-*N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}acetamide



To a stirred suspension of 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-hydroxy-1-methylethyl)-3,4-dihydroquinazolin-2(1*H*)-one (460mg) in acetic acid (0.4mL) was added bromoacetonitrile (0.1mL). To this mixture was added concentrated sulfuric acid (0.2mL) and the resulting solution was allowed to stir overnight. The reaction was quenched by dropwise addition of the mixture to a rapidly stirred mixture of 2N aqueous NaOH and CH_2Cl_2. Transferred to a separatory funnel, diluted with water and extracted 3x with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography on silica gel eluting with 2:1 hexanes/acetone giving 2-bromo-*N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}acetamide. Mass spectrum (ESI) 580 (M+1); 582 (M+3); 584 (M+5). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta$$CHCl_3$ 7.55-7.50 (3H, m); 7.40-7.34 (4H, m); 6.91 (1H, d, J=1.9Hz); 6.55 (1H, br s); 6.16 (1H, d, J=1.9 Hz); 5.17 (1H, br s); 4.41 (1H, ½ dd, J=14.4 Hz, J = 1.6 Hz); 4.27 (1H, dd, J = 14.4, Hz, J = 1.6 Hz); 3.73 (1H, ½ ABq, J= 13.6 Hz); 3.68 (1H, ½ ABq, J = 13.6); 1.64 (3H, s); 1.57 (3H, s).

EXAMPLE DDD3

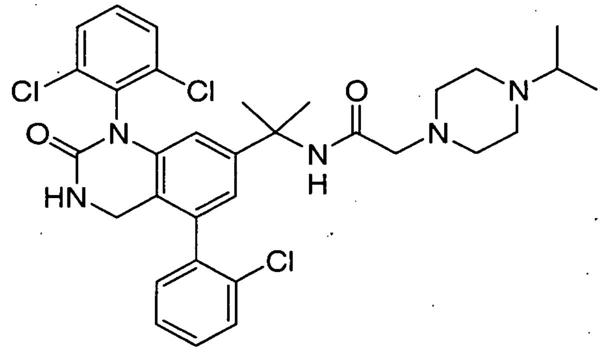
<u>*N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-2-morpholin-4-ylacetamide</u>



To a stirred solution of 2-bromo-*N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}acetamide (30mg, 0.05mmol, 1eq) in DMF (0.5mL) was added morpholine (0.01mL) and diisopropylethylamine (0.02mL). The mixture was warmed to and maintained at 80°C for 1.5h at which time HPLC analysis indicated complete reaction. The mixture was diluted with ethyl acetate and washed 3x with dilute NaOH. The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated giving *N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-2-morpholin-4-ylacetamide. Mass spectrum 587.2 (M+1); 589.2 (M+3).

EXAMPLE DDD4

N-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-2-(4-isopropylpiperazin-1-yl)acetamide

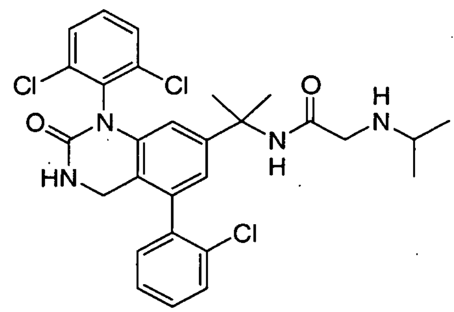


The title compound was made according to the procedure outlined in **EXAMPLE DDD3** using isopropylpiperazine. The product was purified by preparative reverse phase HPLC [Waters Xterra C8ms 19x100 mm column using a gradient elution of 90% water (+ 0.1% TFA)/10% CH_3CN (+ 0.1% TFA) to 100% CH_3CN (+ 0.1% TFA) over 12min at 20mL/min] giving *N*-{1-[5-(2-chlorophenyl)-1-

(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-2-(4-isopropylpiperazin-1-yl)acetamide as the TFA salt. ^{1}H NMR (500 MHz, $CDCl_3$): δ$CHCl_3$ 7.53-7.49 (3H, m); 7.39-7.34 (4H, m); 6.90 (1H, d, J = 1.2 Hz); 6.15 (1H, d, J = 1.2 Hz); 5.18 (1H, br s); 4.408 (1H, dd, J = 14.4 Hz, J = 1.2 Hz); 4.26 (1H, dd, J = 14.4 Hz, J = 1.4 Hz); 2.84 (1H, ½ ABq, J = 16.3 Hz); 2.79 (1H, ½ ABq, J = 16.3 Hz); 2.65 (1H, m); 2.47 (8H, br s); 1.61 (3H, s); 1.56 (3H, s); 1.06 (6H, m).

COMPOUND DDD-4

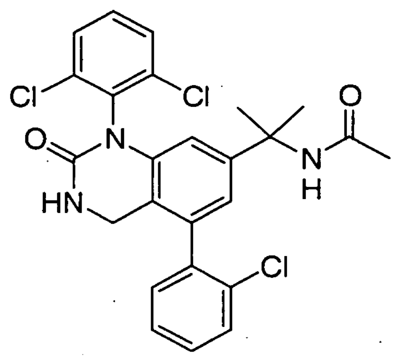
N^1-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-N^2-isopropylglycinamide



The title compound was made according to the procedure outlined in **EXAMPLE DDD3** using isopropylamine. The product was purified by preparative reverse phase HPLC [Waters Xterra C8ms 19x50 mm column using a gradient elution of 90% water (+ 0.1% TFA)/10% CH_3CN (+ 0.1% TFA) to 100% CH_3CN (+ 0.1% TFA) over 12min at 20mL/min] giving N^1-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-N^2-isopropylglycinamide as the TFA salt. Mass spectrum (ESI) 559.1 (M+1); 561.1 (M+3).

COMPOUND DDD-5

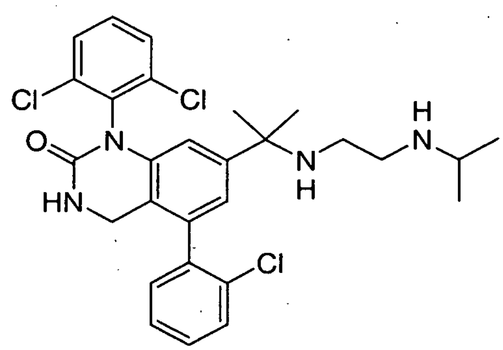
N-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}acetamide



The title compound was prepared according to the procedure outlined in **COMPOUND DDD-3** using acetonitrile instead of bromoacetonitrile. The product was purified by flash column chromatography on silica gel eluting with 2:1 hexanes/acetone and then by preparative thin layer chromatography eluting 3x with 3.5% MeOH in CH_2Cl_2 to give *N*-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}acetamide. Mass spectrum (ESI) 502 (M+1); 504 (M+3).

COMPOUND DDD-6

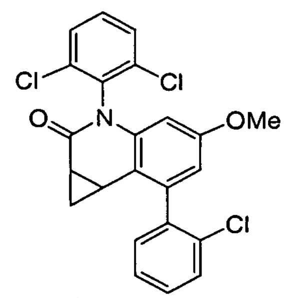
5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-{[2-(isopropylamino)ethyl]amino}-1-methylethyl)-3,4-dihydroquinazolin-2(1*H*)-one



Dissolved N^1-{1-[5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl]-1-methylethyl}-N^2-isopropylglycinamide (**COMPOUND DDD-4**) (53mg) borane-THF solution (3mL of a 1M solution). The mixture was brought to and maintained at reflux for 4h. The mixture was cooled. Aqueous 6N HCl (6mL) was added and the mixture was heated to 80°C for 30min. The reaction was cooled and diluted with ethyl acetate. The aqueous layer was made basic by addition of 2N NaOH. The layers were mixed and then separated. The ethyl

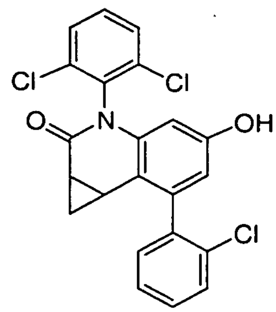
acetate layer was washed with aqueous 2N NaOH. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by preparative reverse phase HPLC [Waters Xterra C8ms 19x50mm column using a gradient elution of 90% water (+ 0.1% TFA)/10% CH_3CN (+ 0.1% TFA) to 100% CH_3CN (+ 0.1% TFA) over 12min at 20mL/min] giving 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-7-(1-{[2-(isopropylamino)ethyl]amino}-1-methylethyl)-3,4-dihydroquinazolin-2(1*H*)-one. Mass spectrum (ESI) 545 (M+1); 547 (M+3).

COMPOUND NAN-1



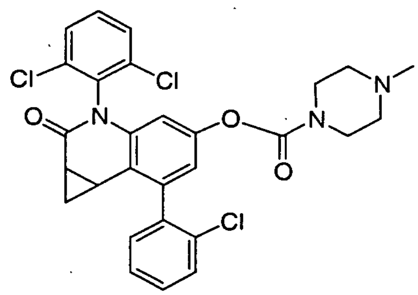
Oil free sodium hydride (36mg) suspended in dry DMSO (5mL) was added trimethylsulfoxonium chloride (193mg) at room temperature. After bubbling subsided, the **INTERMEDIATE 8** (300mg) in DMSO (5mL) was added to reaction mixture. The solution was stirred at rt for 1h and at 60°C for 18h. The mixture was partitioned between ethyl acetate and water. The two layers were separated and the organic phase was washed with water (3x), brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel (hexanes/ethyl acetate=2/1) to give **COMPOUND NAN-1**. ^1H NMR($CDCl_3$, 500MHz, diastereomers): 7.53 (m, 3H), 7.39 (m, 4H), 6.53 (d, 1H, one diastereomer), 6.48 (d, 1H, one diastereomer), 5.70(d, 1H, diastereomers mixture), 3.68 (s, 3H, one diastereomer), 3.51 (s, 3H, one diastereomer), 2.20 (m, 2H), 1.65 (m, 1H), 1.07 (m, 1H, one diastereomer), 0.97 (m, 1H, one diastereomer). MS(ES) 444 (M+H).

COMPOUND NAN-2



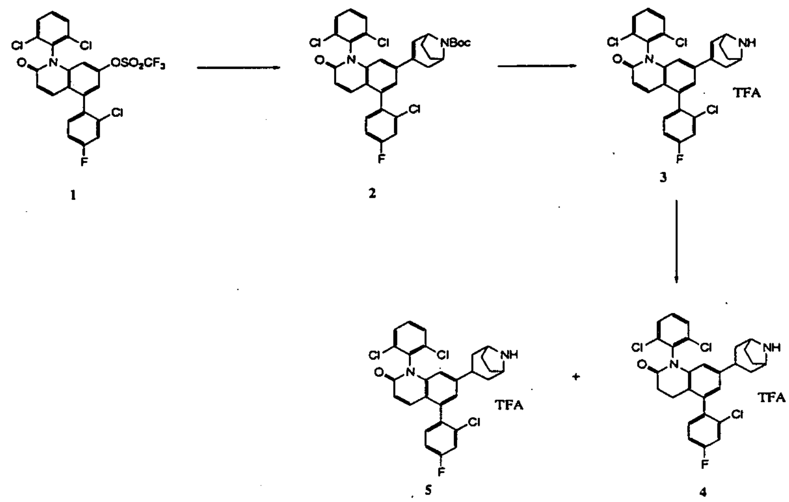
The title compound was prepared as described above in **INTERMEDIATE 3**. MS(ES) 430 (M+H).

EXAMPLE NAN1

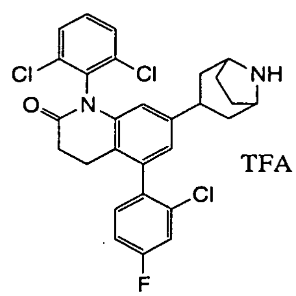


To a solution of **COMPOUND NAN-2** (43mg) in dichloromethane was added diisopropylethylamine (0.17mL) and phosgen (0.5mL, 1.9 M in toluene)at –20°C. The mixture was warmed up to rt and stirred for 16h. The solution was concentrated to dry to give crude mixture. To a solution of this crude mixture in dichloromethane was added 1-methylpiperazine and diisopropylethylamine at rt and stirred for 16h. Removal of the solvent and subsequent purification by preparative thin layer chromatography (hexanes/ethyl acetate=1/1) provided the title product. ^{1}H NMR($CDCl_3$, 500MHz, diastereomers): 7.52 (m, 3H), 7.40 (m, 4H), 6.79 (d, 1H, one diastereomer), 6.76 (d, 1H, one diastereomer), 5.70 (d, 1H, one diastereomer), 5.88 (d, 1H, one diastereomer), 3.63 (m, 4H), 2.47 (m, 4H), 1.71 (m, 1H, one diastereomer), 1.57 (m, 1H, one diastereomer), 1.10 (m, 1H, one diastereomer), 1.02 (m, 1H, one diastereomer). MS(ES) 556 (M+H).

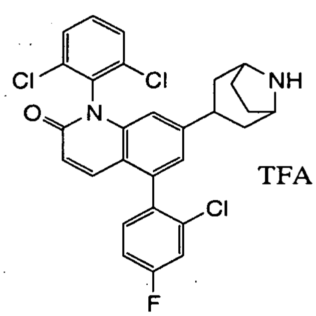
EXAMPLE MMM1A and
EXAMPLE MMM1B



EXAMPLE MMM1A



EXAMPLE MMM1B



Step A: A mixture of **1** (232mg, 0.409mmol), LiCl (69mg, 1.64mmol), $Pd(PPh_3)_4$ (47mg, 0.041mmol) and tin reagent (228mg, 0.61mmol) in 5mL of dioxane was heated under N_2 at 110°C for 19h. Solvent was removed and the residue was purified by flash chromatography EtOAc/Hexane = 1:4 to give **2**.

Step B: Compound **2** (0.2379g, 0.38mmol) was stirred in 5mL of trifluoroacetic acid for 30min. Then, volatiles were removed by vacuum to give **3** as TFA salt. Mass spectrum (ESI) 527 (M+1).

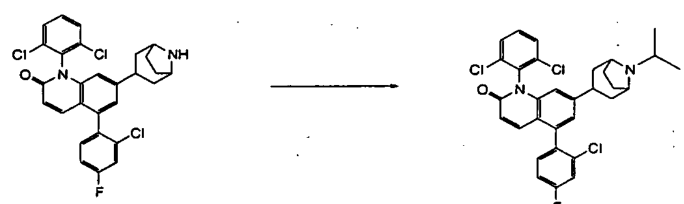
Step C: A solution of **3** (217.5mg, 0.34mmol) and PtO_2 (100mg) in 10mL of acetic acid was shaken under 40PSI of H_2 for 6.5h. Solvent was removed by vacuum and the residue was taken in CH_2Cl_2 and filtered through a plug of Celite. The crude was purified by reverse phase HPLC to give **5 (EXAMPLE MMM1A)** and **4 (EXAMPLE MMM1B)**. Mass spectrum (ESI) for **5**, 529 (M+1). Mass spectrum (ESI) for **4**, 531 (M+1).

EXAMPLE MMM2

1 2

A mixture of **1** (23.3mg, 0.036mmol), HOAc (0.016mL, 0.29mmol) and HCHO (0.024mL, 0.29mmol) in 2mL of THF was added CH_3CN (2mL) and $NaB(OAc)_3H$ (91mg, 0.43mmol). After stirring at rt for 4h, it was removed of volatiles and was purified by HPLC to give **2 (EXAMPLE MMM2)**. Mass spectrum (ESI) for **2**, 543 (M+1).

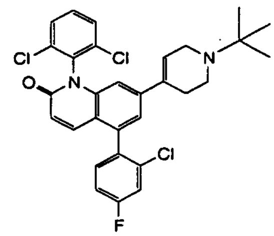
EXAMPLE MMM3



1 2

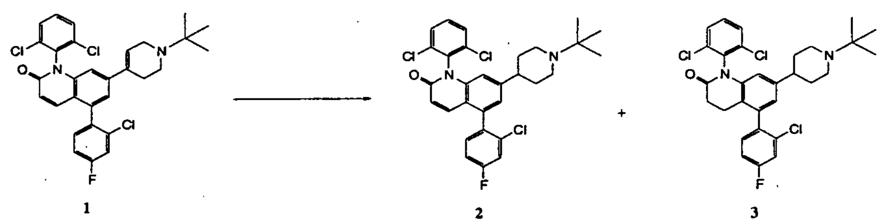
A solution of **1** (23.3mg, 0.036mmol), acetone (0.026mL, 0.36mmol) in CH_2Cl_2 was added Et_3N (0.020mL, 0.144mmol) and $Na(OAc)_3H$ (15.2mg, 0.072mmol) and the mixture was stirred at rt for 24h. Volatiles were removed and the residue was purified by HPLC to give **2 (EXAMPLE MMM3)**. Mass spectrum (ESI) for **2**, 571 (M+1).

EXAMPLE MMM4



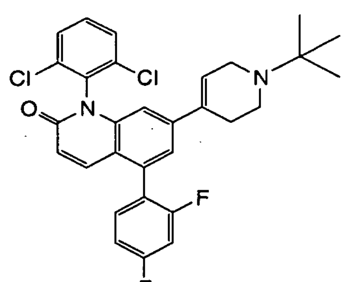
The title compound was prepared as **EXAMPLE MMM1A, Step A.** Mass spectrum (ESI), 557 (M+1).

EXAMPLE MMM5A and EXAMPLE MMM5B



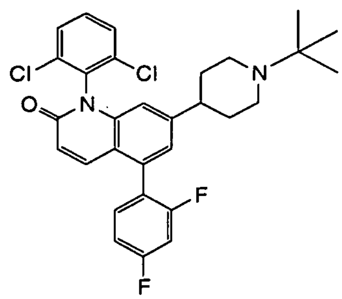
This reaction was carried out similarly as **EXAMPLE MMM1A and MMM1B, Step C**. Mass spectrum (ESI) for **2 (EXAMPLE MMM5A)**, 559 (M+1). Mass spectrum (ESI) for **3 (EXAMPLE MMM5B)**, 561 (M+1).

EXAMPLE MMM6



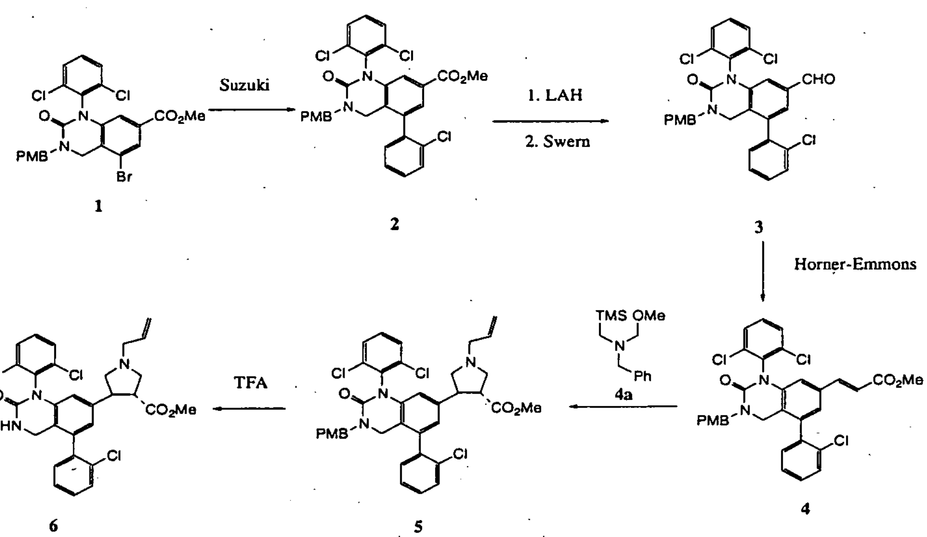
This reaction was carried out similarly as **EXAMPLE MMM1A, Step A.** Mass spectrum (ESI) for the title compound, 539 (M+1).

EXAMPLE MMM7



This reaction was carried out as **EXAMPLE MMM1A, Step C** except that the reaction was carried out with the H_2 pressure of 19PSI for 15min in a mixture of EOAc and methanol (9:1). Mass spectrum (ESI) for the title compound, 541 (M+1).

EXAMPLE MMM8



Step A: A mixture of **1** (1.516g, 2.76mmol), $Pd(OAc)_2$ (0.0186g, 0.083mmol) and PPh_3 in 15mL of DME was purged with N_2 for 5min. After the solution was stirred rt for 10min, Na_2CO_3 (8.3mmol, as 2M solution) was added and the solution was degassed again and stirred at rt for 1h. Then 2-chlorophenylboronic (0.646g, 4.13mmol) was added and the solution was degassed again. The resulting solution was heated at 104^oC for 4h and was then poured into CH_2Cl_2. The solution was washed once with water, dried with Na_2SO_4 and filtered. The crude was purified by flash chromatography with EtOAc/hex = 1:4 to 3:7 to give **2**. Mass spectrum (ESI) for **2**, 581 (M+1).

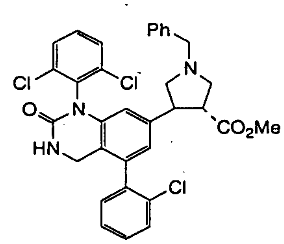
Step B: A solution of **2** (0.89g, 1.53mmol) in 30mL of THF was added LAH (1.42mL, 1.42mmol) at 0^{o}C and the solution was allowed to stirred for 1.5h. The reaction was quenched by adding $Na_2SO_4 \cdot 10H_2O$ until no more gas was formed. The solution was filtered through Celite and evaporated to give alcohol.

Step C: A solution of oxalyl chloride (0.27mL, 3.06mmol) in CH_2Cl_2 was added DMSO (0.43mL, 6.12mmol) at -78^{o}C. After 5min, the above alcohol (0.85g, 1.53mmol) in 5mL of CH_2Cl_2 was added and was followed by Et_3N (1.07mL, 7,65mmol). The mixture was allowed to warm up to rt for 30min and was then poured into ether. The solution was washed with brine, dried with Na_2SO_4 and filtered to afford **3**.

Step D: A solution of trimethyl phosphate (0.22mL, 1.84mmol) in 20mL was added LHMDS (1.84mL as 1M solution) at 0^{o}C. After 40min, the solution was cooled to -78^{o}C and the aldehyde **3** (0.85g, 1.54mmol) in 10mL of THF was added. The solution was allowed to warmed slowly to rt overnight and was poured into ether. The solution was washed with $NaHCO_3$ (1x) and brine (1x), dried with Na_2SO_4. The crude was purified with EtOAc/hexane = 3:7 to give 4. Mass spectrum (ESI) for **4**, 609 (M+1).

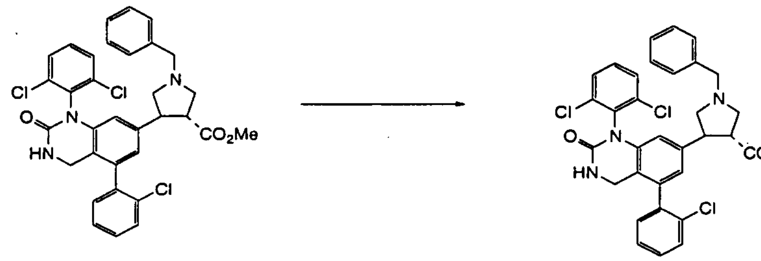
Step E: A solution of **4** in 15mL of CH_2Cl_2 was added trifluoroacetic acid (0.014mL, 0.18mmol) at 0^{o}C and solution was allowed to warmed to rt slowly overnight. The mixture was poured into CH_2Cl_2 and was washed with $NaHCO_3$, dried with Na_2SO_4. Mass spectrum (ESI) for **5**, 692 (M+1). The crude was dissolved in 4mL of TFA and stirred for 2.5h. Solvent was removed and was dissolved in CH_2Cl_2. The solution was washed once with 2N NaOH, dried with Na_2SO_4 and was purified with flash chromatography with acetone/ hexane = 1:4 to give **6** **(EXAMPLE MMM8)**. Mass spectrum (ESI) for **6**, 572 (M+1).

EXAMPLE MMM9



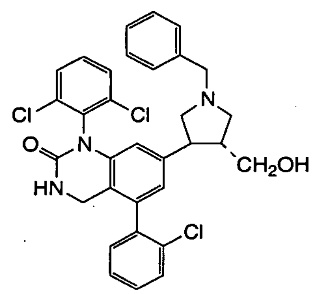
This compound was prepared similarly as **EXAMPLE MMM8**. Mass spectrum (ESI, 622 (M+1).

EXAMPLE MMM10



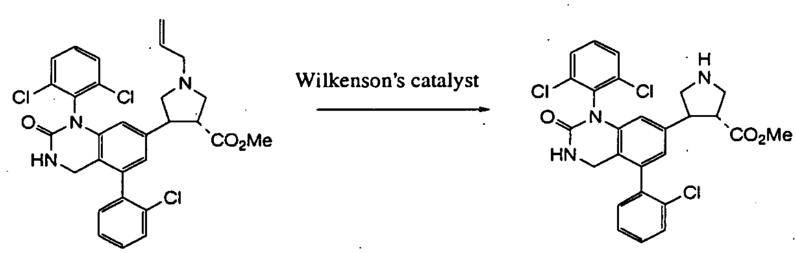
Ester **1** (26mg, 0.042mmol) and LiOH·H_2O (17.6mg, 0.42mmol) in 1.5mL of methanol was added 0.5mL of H_2O and the resulting solution was stirred at rt for 3h. Upon removal of volatiles, the crude was purified by HPLC to give the title compound. Mass spectrum (ESI), 608 (M+1).

EXAMPLE MMM11



The title compound was prepared similarly as **EXAMPLE MMM8, Step B**. Mass spectrum (ESI), 592 (M+1).

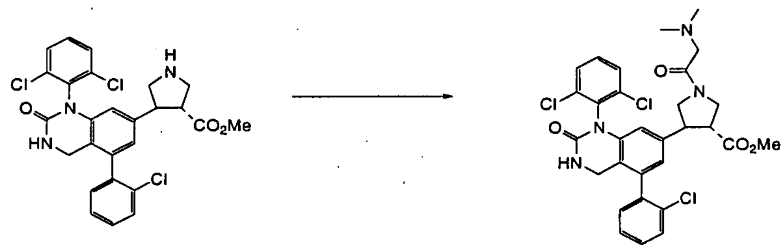
EXAMPLE MMM12



Compound **1** (1.18g, 2.10mmol) in 13.6mL of CH_3CN was added $(Ph_3P)_3RhCl$ (95mg, 0.10mmol) and H_2O (2.4mL) and the solution was degassed with N_2 for 5min. The mixture was then heated at reflux for 3h with a Dean-Stark

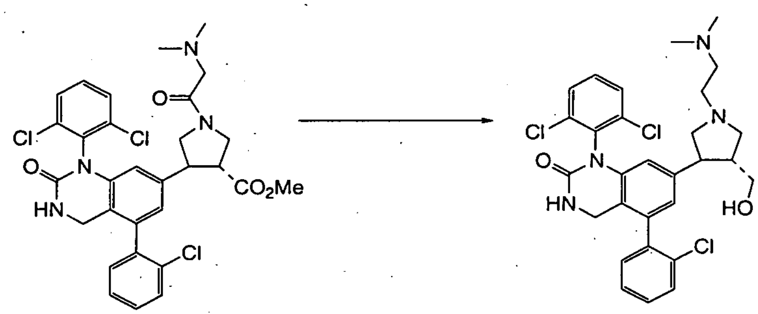
trap. After removal of solvents, the crude was purified by purified with flash chromatography with CH_2Cl_2/ $MeOH/NH_3.H_2O$ = 100:4:0.8 to give the title compound. Mass spectrum (ESI), 530 (M+1).

EXAMPLE MMM13



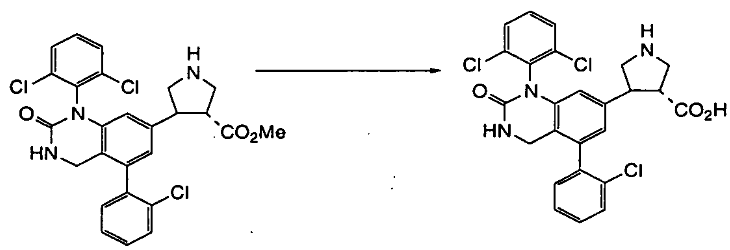
A solution of **1** (40mg, 0.075mmol), N,N-dimethylglycine (10.9mg, 0.105mmol), EDC (23.1mg, 0.121mmol) and DMAP (18.3mg, 0.15mmol) in 3mL of CH_2Cl_2 was stirred at rt for 16h. After removal of solvent, the crude was purified by HPLC to give the title compound, Mass spectrum (ESI), 615 (M+1).

EXAMPLE MMM14



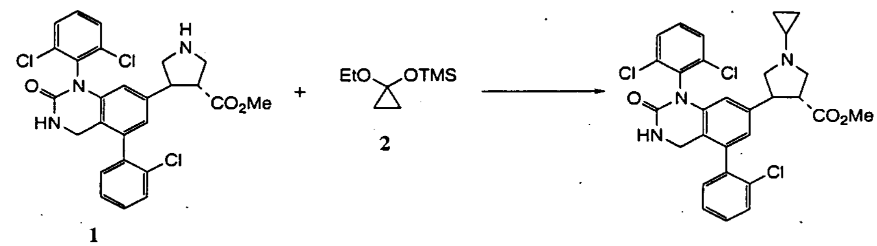
The title compound was prepared similarly as **EXAMPLE MMM8, Step B.** Mass spectrum (ESI), 575 (M+1).

EXAMPLE MMM15



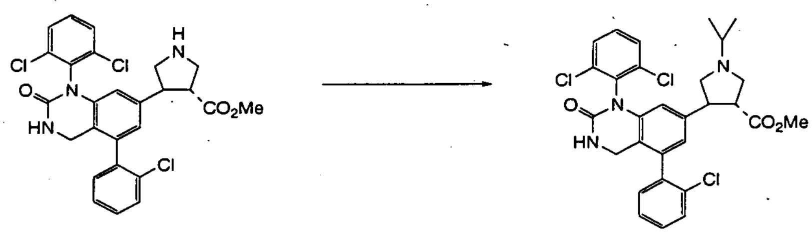
The title compound was prepared similarly as **EXAMPLE MMM10**, from the ester. Mass spectrum (ESI), 518 (M+1).

EXAMPLE MMM16



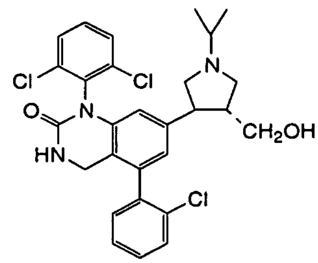
A solution of **1** (29.1mg, 0.055mmol), 2 (0.066mL, 0.33mmol) in 3mL of MeOH was added $NaBH_3CN$ (15.6mg, 0.25mmol) and HOAc (0.031mL, 0.55mmol) and the solution was heated at 100oC for 3h. It was poured into CH_2Cl_2 and was washed with 2N NaOH once, dried over Na_2SO_4 and purified by HPLC to give the title compound. Mass spectrum (ESI), 572 (M+1).

EXAMPLE MMM17



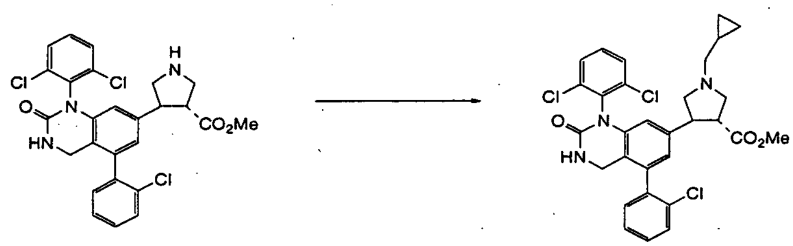
A solution of **1** (53.9mg, 0.10mmol), acetone (0.0298mL, 0.41mmol) in 3mL of CH_2Cl_2 was added $NaBH_3CN$ (25.6mg, 0.41mmol) was stirred at rt overnight and was poured into CH_2Cl_2. The solution was washed with 2N NaOH, dried with Na_2SO_4 and purified by HPLC to give the title compound, Mass spectrum (ESI), 574 (M+1).

EXAMPLE MMM18



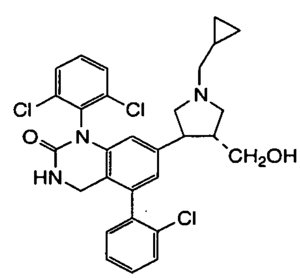
The title compound was prepared similarly as **EXAMPLE MMM8, Step B.** Mass spectrum (ESI), 544 (M+1).

EXAMPLE MMM19



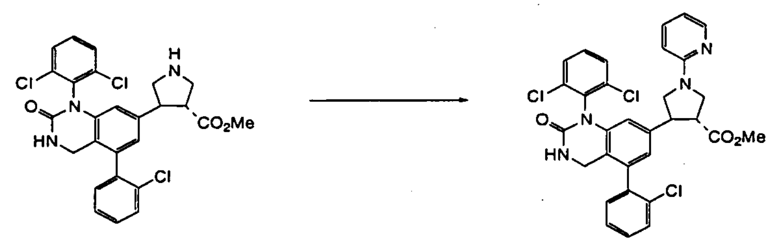
A solution of **1** (50.3mg, 0.095mmol), (bromomethyl)cyclopropane (0.055mL, 0.57mmol) in 2mL of EtOH was added triethylamine (0.132 ml, 0.95mmol) and the solution was heated at 70^{o}C for 14h. After removal of volatiles, it was purified by HPLC to give the title compound. Mass spectrum (ESI), 586 (M+1).

EXAMPLE MMM20



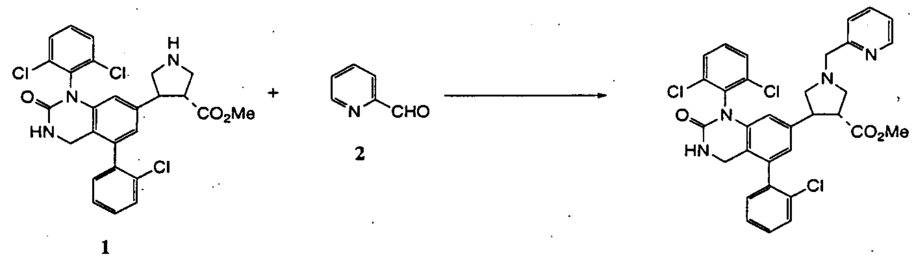
The title compound was prepared similarly as **EXAMPLE MMM8.** Mass spectrum (ESI), 556 (M+1).

EXAMPLE MMM21



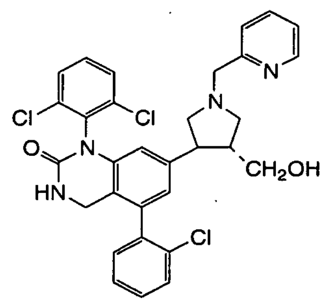
A solution of 1 (50.3mg, 0.095mmol), 2-fluoropyridine (0.016mL, 0.19mmol) and K_2CO_3 (39.4mg, 0.285mmol) in 4 ml of DMF was heated at 120°C for 16h. After removal of volatiles, it was purified by HPLC to give the title compound. Mass spectrum (ESI), 609 (M+1).

EXAMPLE MMM22



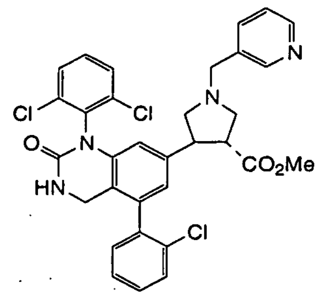
A solution of **1** (61.6mg, 0.12mmol), 2 (0.016mL, 0.41mmol) in 4mL of CH_2Cl_2 was added $NaB(OAc)_3H$ (49.2mg, 0.23mmol) was stirred at rt overnight and the crude was purified by preparative TLC to give the title compound, Mass spectrum (ESI), 623 (M+1).

EXAMPLE MMM23



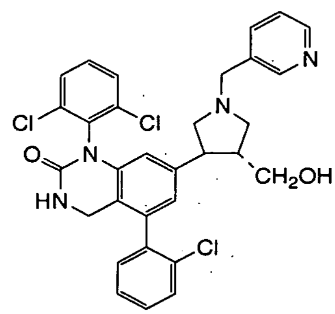
The title compound was prepared similarly as **EXAMPLE MMM8, Step B.** Mass spectrum (ESI), 593 (M+1).

EXAMPLE MMM24



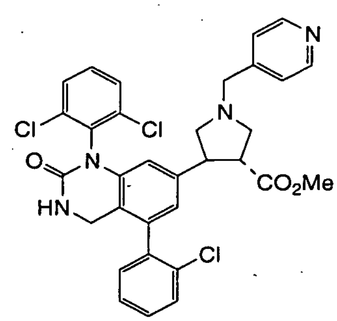
The title compound was prepared similarly as **EXAMPLE MMM17.** Mass spectrum (ESI), 623 (M+1).

EXAMPLE MMM25



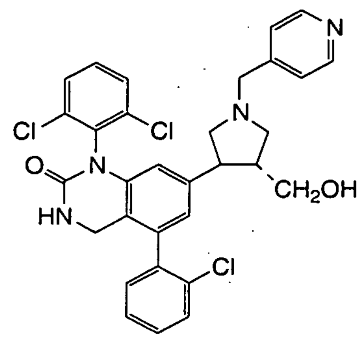
The title compound was prepared similarly as **EXAMPLE MMM8, Step B**. Mass spectrum (ESI), 593 (M+1).

EXAMPLE MMM26



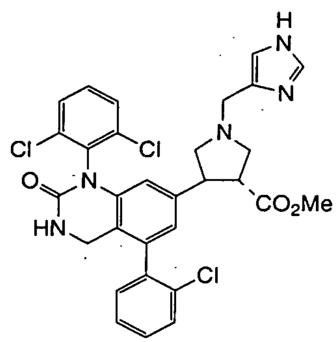
The title compound was prepared similarly as **EXAMPLE MMM17.** Mass spectrum (ESI), 623 (M+1).

EXAMPLE MMM27



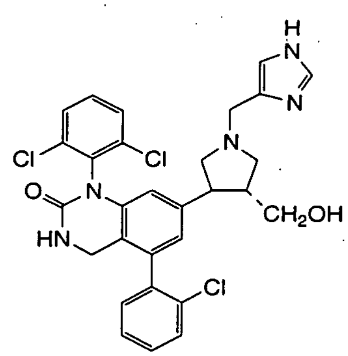
The title compound was prepared similarly as **EXAMPLE MMM8, Step B**. Mass spectrum (ESI), 593 (M+1).

EXAMPLE MMM28



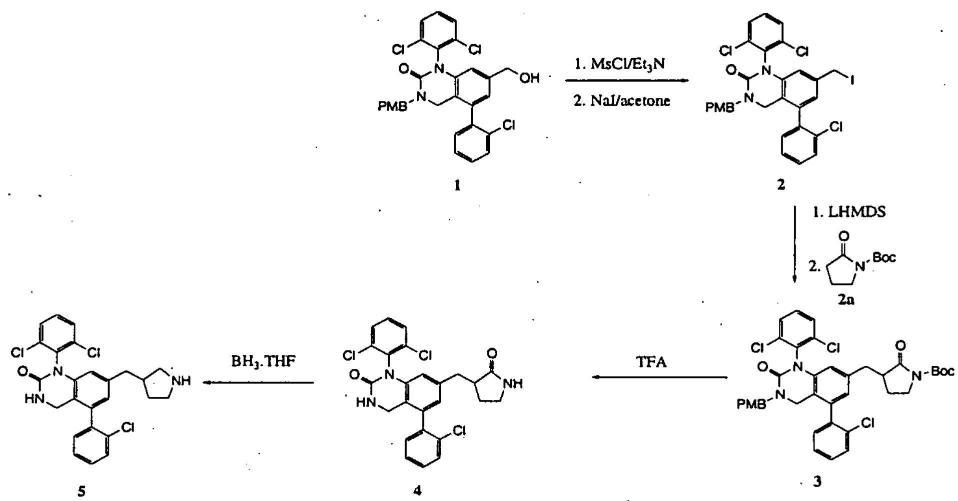
The title compound was prepared similarly as **EXAMPLE MMM17.** Mass spectrum (ESI), 612 (M+1).

EXAMPLE MMM29



The title compound was prepared similarly as **EXAMPLE MMM8, Step B**. Mass spectrum (ESI), 582 (M+1).

EXAMPLE MMM30



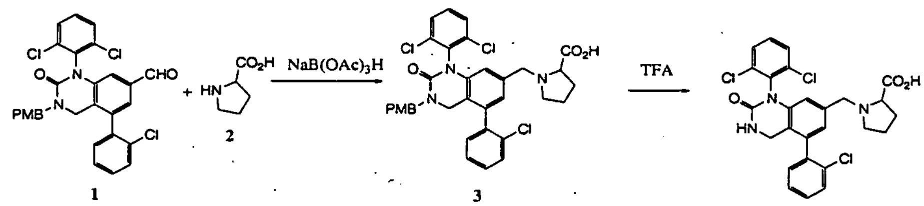
Step A: A solution of **1** (1.01g, 1.83mmol) in 20mL of CH_2Cl_2 was added Et_3N (0.51mL, 3.65mmol) and MsCl (0.21mL, 2.74mmol) at 0°C and was stirred for 1h. It was poured into ether and was washed with $NaHCO_3$ and brine. The organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was dissolved in 30mL of acetone and the solution was added NaI (1.097g, 7.32mmol). After it was heated at reflux for 6h, acetone was removed. The residue was dissolved in ether and was washed with $NaHCO_3$, dried with Na_2SO_4 and purified with flash chromatography EtOAc/hexane = 3:7 to give **2**. Mass spectrum (ESI), 665 (M+1).

Step B: A solution of **2a** (0.030mL, 0.18mmol) in 2mL of THF was added LHMDS (0.21mL as 1M solution in THF) at -78°C. After 20min, **2** (117mg, 0.18mmol) was added at -78°C and the solution was allowed to warmed to rt slowly overnight. It was poured into CH_2Cl_2, washed with $NaHCO_3$ and dried with Na_2SO_4. It was purified by preparative TLC with acetone/hexane = 1:2 to give **3**.

Step C: A solution of **3** in TFA was heated at 90°C for 3.5h and THF was removed. The crude was purified by HPLC to give **4**. Mass spectrum (ESI), 502 (M+1).

Step D: A solution of **4** (21.6mg,, 0.043mmol) in 3mL of THF was added $BH_3 \cdot THF$ (0.173mL as 1M solution) and the mixture was heated at reflux for 3h. The crude was purified by HPLC to give **5 (EXAMPLE MMM30)**. Mass spectrum (ESI), 488 (M+1).

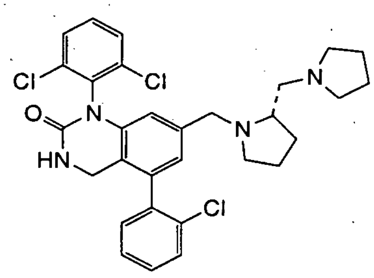
EXAMPLE MMM31



Step A: Compound **3** was prepared similarly as **EXAMPLE MMM17**, Mass spectrum (ESI), 652 (M+1).

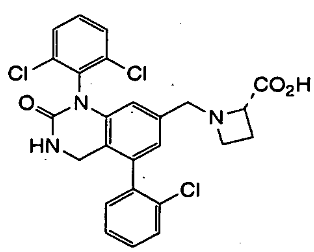
Step B: EXAMPLE MMM31 was prepared from **3** similarly as **EXAMPLE MMM8, Step E**. Mass spectrum (ESI), 532 (M+1).

EXAMPLE MMM32



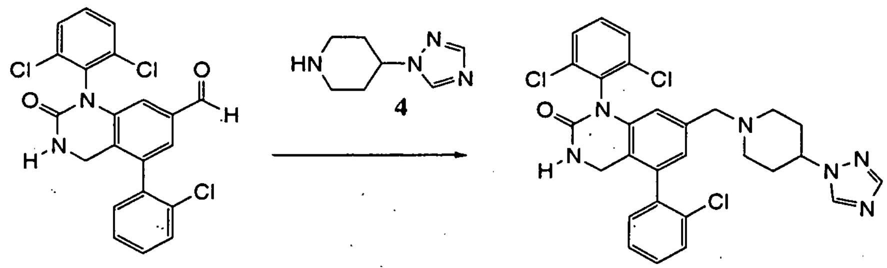
The title compound was prepared similarly as **EXAMPLE MMM22**. Mass spectrum (ESI), 571 (M+1).

EXAMPLE MMM33



The title compound was prepared similarly as **EXAMPLE MMM22**. Mass spectrum (ESI), 518 (M+1).

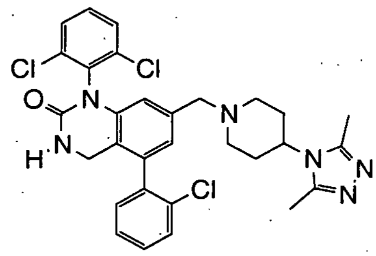
EXAMPLE MMM34



3 5

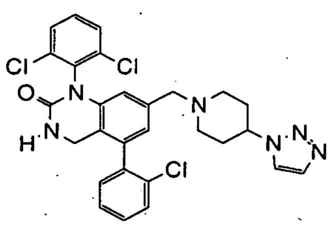
Mass spectrum (ESI) for **5**, 568 (M+1).

EXAMPLE MMM35



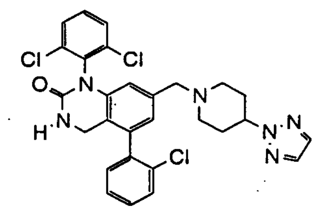
The title compound was prepared similalry as **EXAMPLE MMM34.** Mass spectrum (ESI), 432 (M+1).

EXAMPLE MMM36



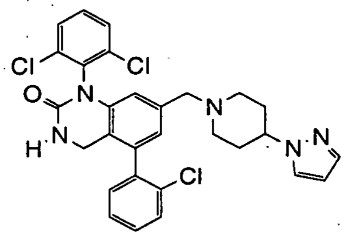
The title compound was prepared similalry as **EXAMPLE MMM34.** Mass spectrum (ESI), 568 (M+1).

EXAMPLE MMM37



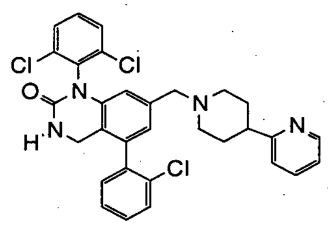
The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI), 568 (M+1).

EXAMPLE MMM38



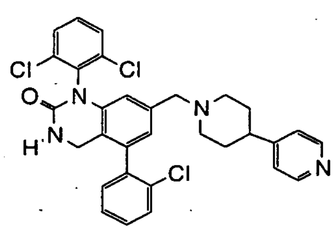
The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI), 567 (M+1).

EXAMPLE MMM39



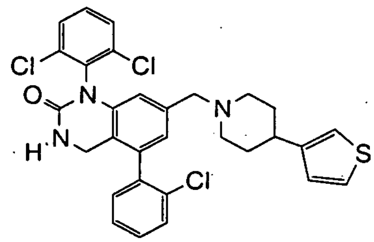
The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI), 578 (M+1).

EXAMPLE MMM40



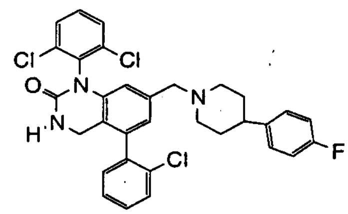
The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI), 578 (M+1).

EXAMPLE MMM41



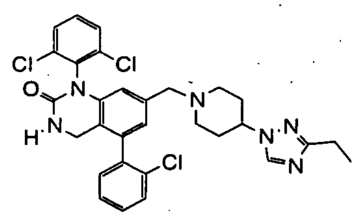
The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI), 583 (M+1).

EXAMPLE MMM42



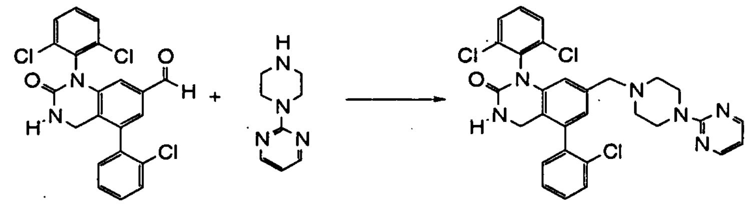
The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 595 (M+1).

EXAMPLE MMM43



The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI), 596 (M+1).

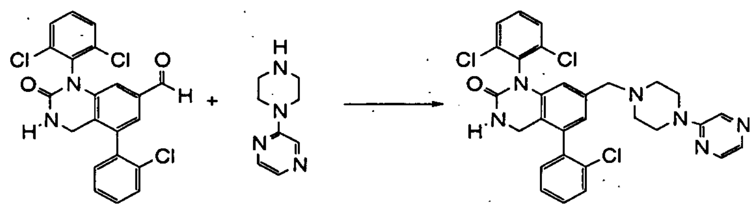
EXAMPLE MMM44



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI), 580 (M+1).

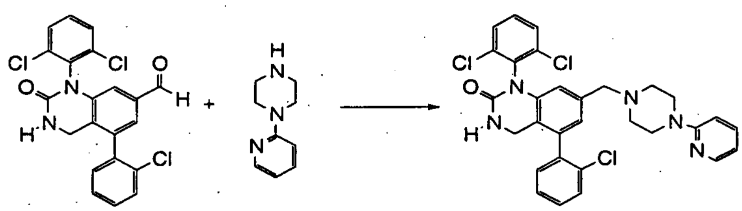
EXAMPLE MMM45



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI) for **3**, 580 (M+1).

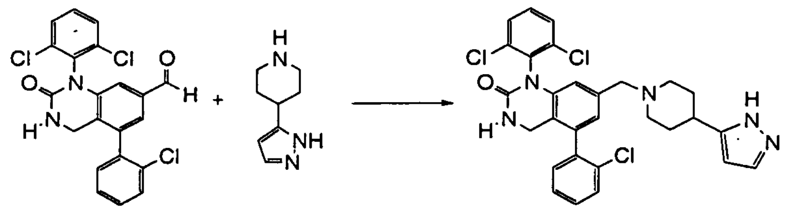
EXAMPLE MMM46



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34**. Mass spectrum (ESI) for **3**, 579 (M+1).

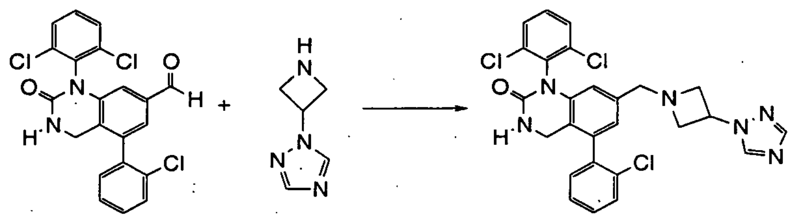
EXAMPLE MMM47



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 567 (M+1).

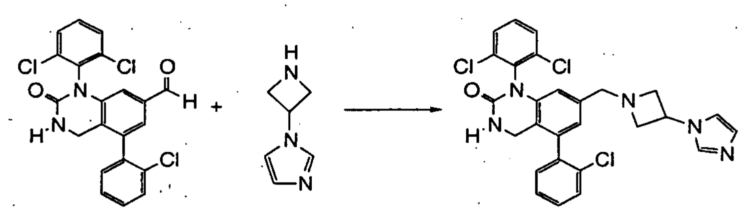
EXAMPLE MMM48



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 541 (M+1).

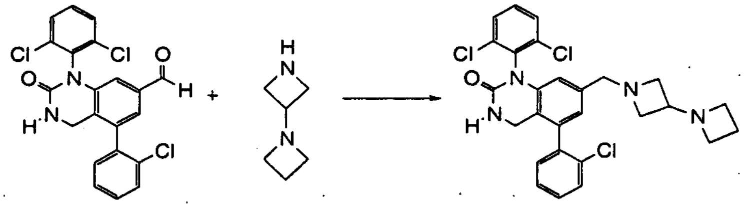
EXAMPLE MMM49



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 568 (M+1).

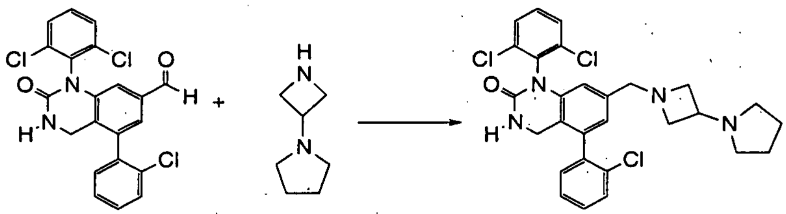
EXAMPLE MMM50



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 528 (M+1).

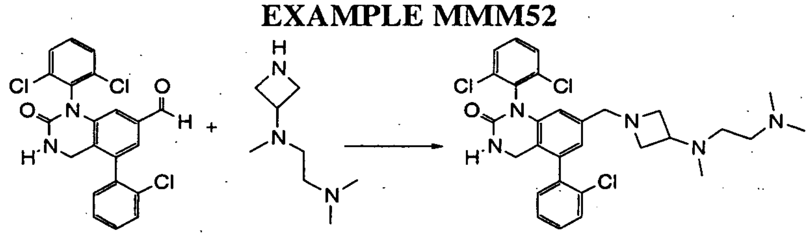
EXAMPLE MMM51



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 542 (M+1).

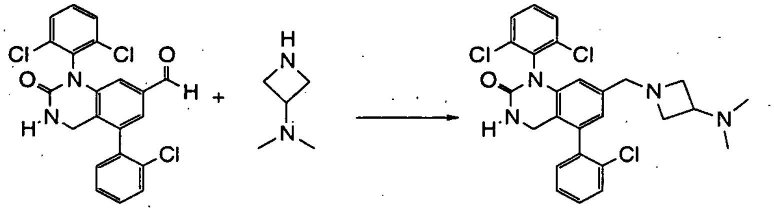
EXAMPLE MMM52



1 2 3

The title compound was prepared similarly as **EXAMPLE MMM34.** Mass spectrum (ESI) for **3**, 573 (M+1).

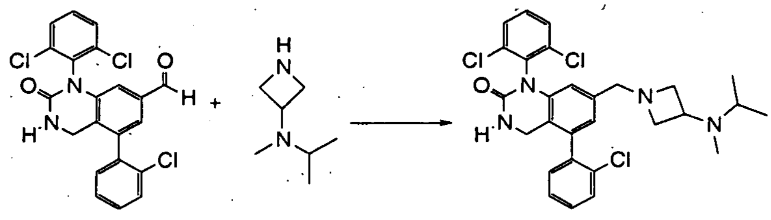
EXAMPLE MMM53



1 2 3

Mass spectrum (ESI) for **3**, 515 (M+1).

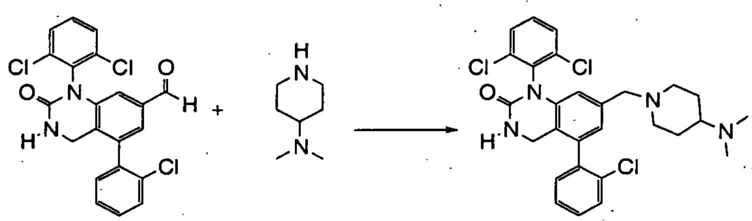
EXAMPLE MMM54



1 2 3

Mass spectrum (ESI) for **3**, 544 (M+1).

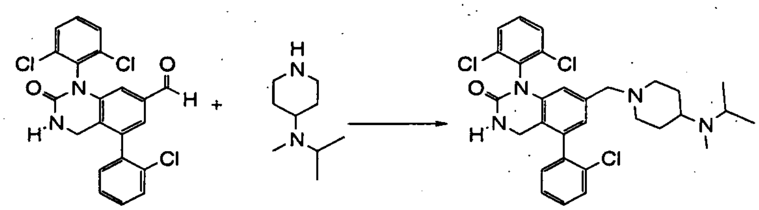
EXAMPLE MMM55



1 2 3

Mass spectrum (ESI) for **3**, 544 (M+1).

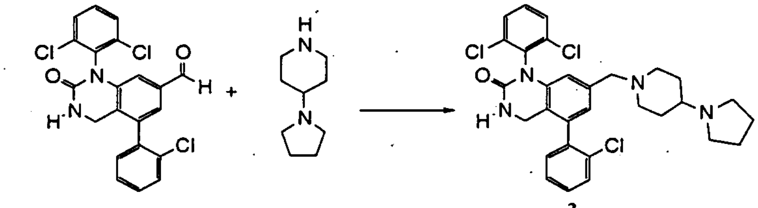
EXAMPLE MMM56



1 2 3

Mass spectrum (ESI) for **3**, 572 (M+1).

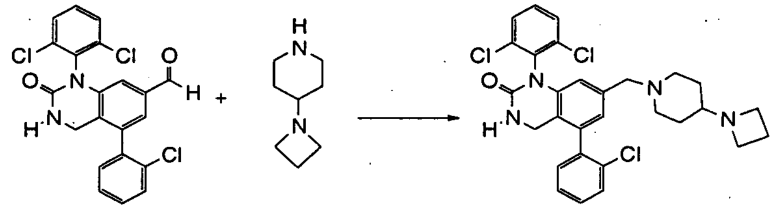
EXAMPLE MMM57



1 2 3

Mass spectrum (ESI) for **3**, 570 (M+1).

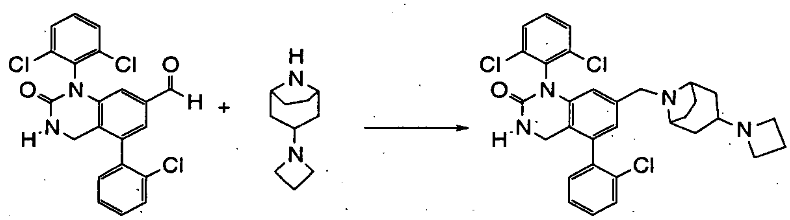
EXAMPLE MMM58



1 2 3

Mass spectrum (ESI) for **3**, 556 (M+1).

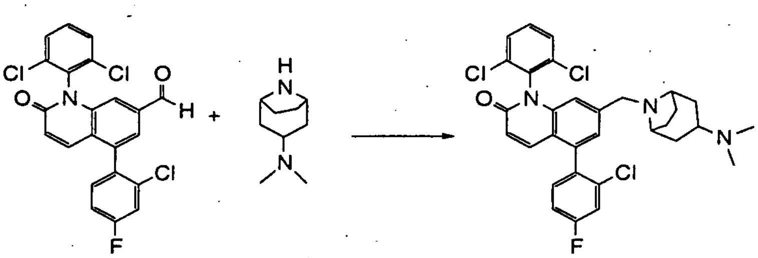
EXAMPLE MMM59



1 2 3

Mass spectrum (ESI) for **3**, 582 (M+1).

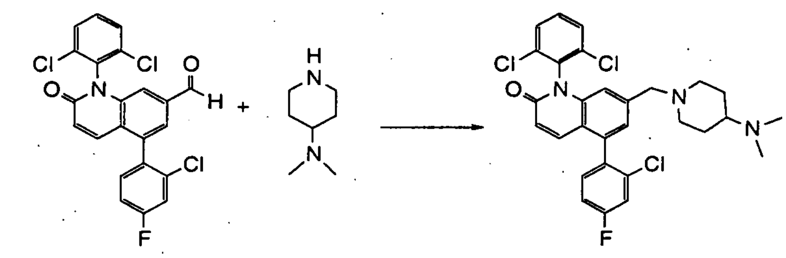
EXAMPLE MMM60



1 2 3

Mass spectrum (ESI) for **3**, 586 (M+1).

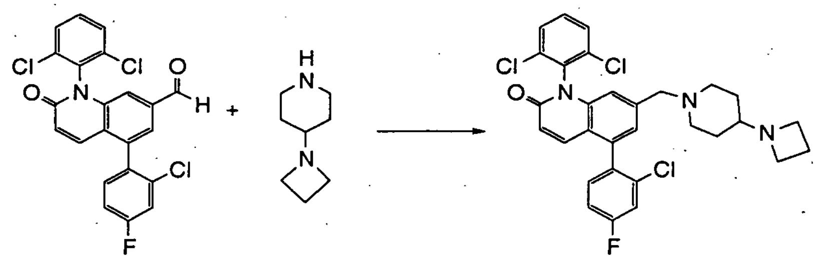
EXAMPLE MMM61



1 2 3

Mass spectrum (ESI) for **3**, 560 (M+1).

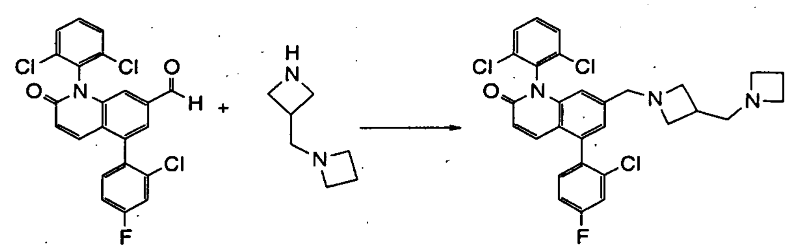
EXAMPLE MMM62



1 2 3

Mass spectrum (ESI) for **3**, 571 (M+1).

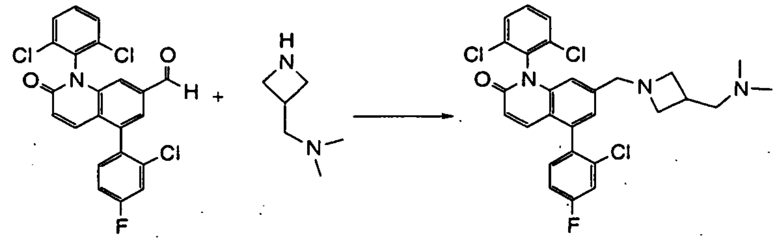
EXAMPLE MMM63



1 2 3

Mass spectrum (ESI) for **3**, 557 (M+1).

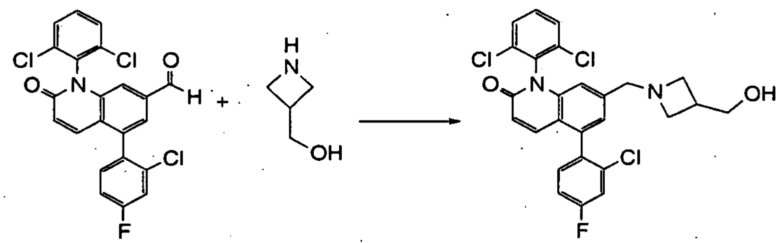
EXAMPLE MMM64



1 2 3

Mass spectrum (ESI) for **3**, 545 (M+1).

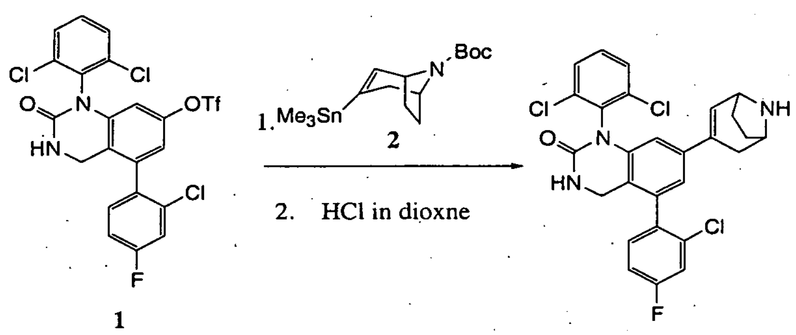
EXAMPLE MMM65



1 2 3

Mass spectrum (ESI) for **3**, 518 (M+1).

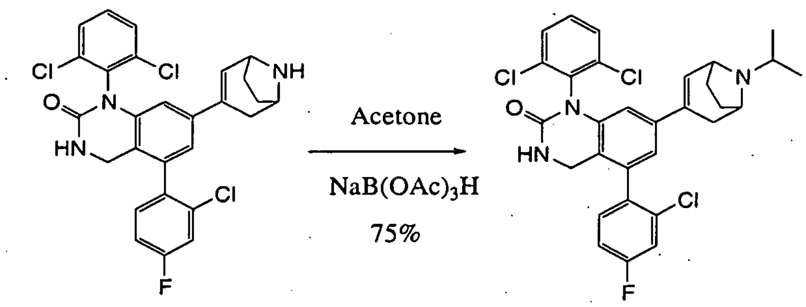
EXAMPLE MMM66



1 3

Mass spectrum (ESI) for **3**, 529 (M+1).

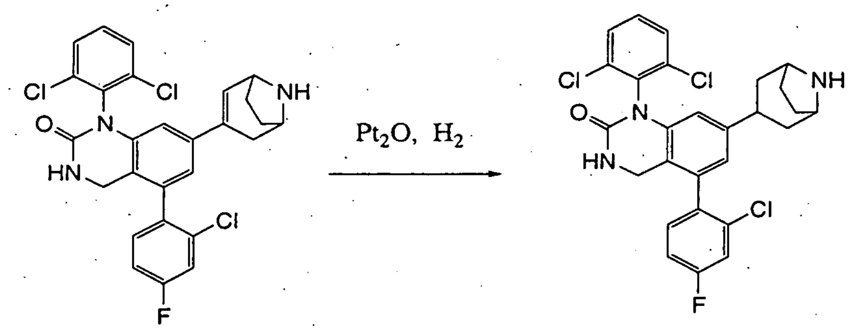
EXAMPLE MMM67



1 2

Mass spectrum (ESI) for **2**, 571 (M+1).

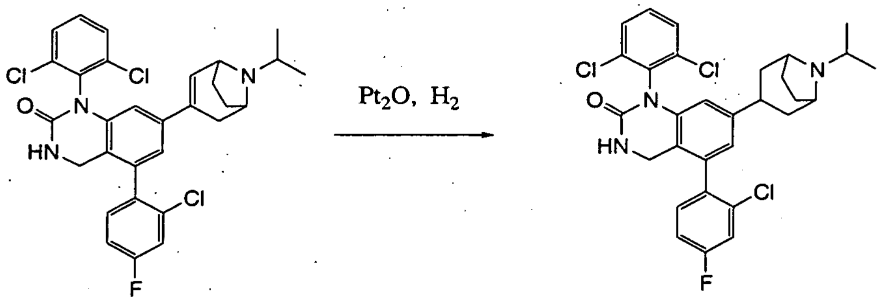
EXAMPLE MMM68



1 2

Mass spectrum (ESI) for **2**, 531 (M+1).

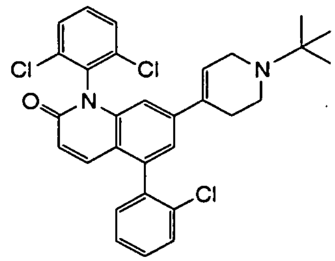
EXAMPLE MMM69



1 2

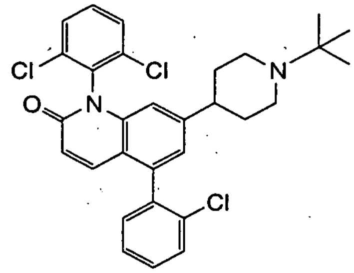
Mass spectrum (ESI) for **2**, 573 (M+1).

EXAMPLE AMM1



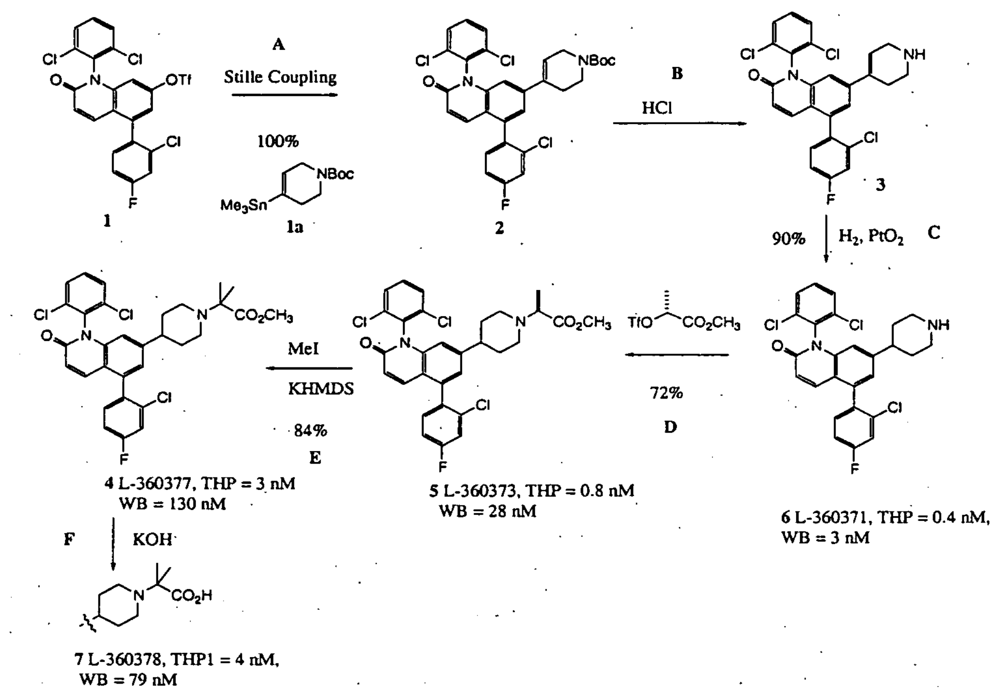
The title compound was prepared as for **EXAMPLE PPP1**. Mass spectrum (ESI), 539 (M+1).

EXAMPLE AMM2



The title compound was prepared as for **EXAMPLE PPP1**. Mass spectrum (ESI), 541(M+1).

EXAMPLE BMM1



Step A: Compound 1 (0.95g, 1.68mmol), 1a (0.76g, 2.19mmol), $Pd(PPh_3)_4$ (0.19g, 0.17mmol) and LiCl (0.28g, 6.72mmol) in 30mL of dioxane were purged with nitrogen for 3 times and the solution was heated at 108^{o}C for 20h. Solvent was removed by vacuum and the residue was dissolved in EtOAc. The organic layer was washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and was purified by flash chromatography EtOAc/hexane = 1:3 to give compound 2. **Step B:** Compound **2** (1.00g, 1.68mmol) in 10mL of CH_2Cl_2 was added solution of HCl in dioxane (6.7mL as 4M solution) and the resulting solution was stirred at rt for 24h. Volatiles were removed by vacuum to give compound **6** as HCl salt. Mass spectrum (ESI), 499 (M+1).

Step C: A solution of the salt **3** (1.68mmol) from the last step in 20mL of EtOAc was added 2.5mL of MeOH and PtO_2 (360mg, 1.59mmol) was shaken on Parr hydrogenator at 3psi for 20min. The solution was filtered through celite. Upon removal of volatiles, the crude was purified by flash chromatography with $CH_2Cl_2/MeOH/NH_4OH$ = 100:10:1 to give compound **6**. Mass spectrum (ESI), 501 (M+1).

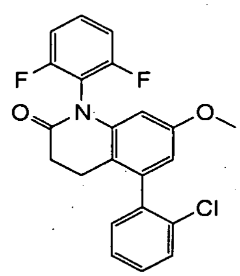
Step D: A solution of R-(+)-methyl lactate (0.043mL, 0.45mmol) in 4mL of CH_2Cl_2 was added 2,6-lutidine (0.064mL, 0.55mmol) and Tf_2O (0.081mL, 0.48mmol) at 0^{o}C. After 0.5h, to the solution was added diisopropylethylamine (0.11mL, 0.64mmol) and compound **6** (0.228g, 0.45mmol) in 4mL of CH_2Cl_2. The solution was then allowed

to stirred at rt for 14h. Volatiles were removed by vacuum and the residue was purified by flash chromatography with Hexanes/EtOAc/2N NH_3 in MeOH = 100:20:4 to give compound **5**. Mass spectrum (ESI), 587 (M+1).

Step E: A solution of **5** (0.104g, 0.177mmol) in 2.5mL of THF was added KHMDS (0.71mL, 0.35mmol as 0.5M in toluene) at -78^{o}C. After 15min, MeI (0.044ml, 0.71mmol) was added and the solution was stirred for 1h. The reaction was quenched with $NaHCO_3$ and warmed to rt. Mixture was poured into CH_2Cl_2 and was washed once with brine. The organic phase was dried with Na_2SO_4 and filtered through Celite. Upon removal of volatiles, the residue was purified by preparative TLC plate with Hexanes/EtOAc/2N NH_3 in MeOH = 100:30:6 to give compound **4.** Mass spectrum (ESI), 601 (M+1).

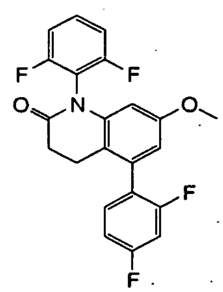
Step F: A solution of **4** (22.4mg, 0.037mmol) in 1.5mL of MeOH was added KOH (20.9mg, 0.37mmol) and 0.5mL of water. The solution was heated at 80^{o}C for 24h. Upon removal of volatiles, the residue was purified by reversed phase HPLC to give compound **7 (EXAMPLE BMM1)**. Mass spectrum (ESI), 587 (M+1).

COMPOUND BMM-1



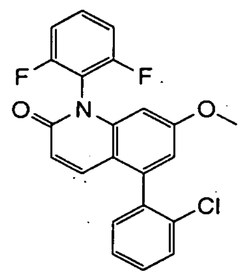
The title compound was prepared similarly as **EXAMPLE PPP1.** Mass spectrum (ESI), 400 (M+1).

COMPOUND BMM-2



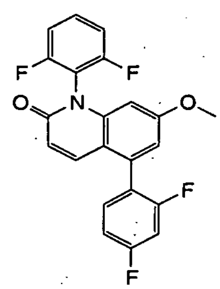
The title compound was was prepared similarly as **EXAMPLE PPP1**. Mass spectrum (ESI), 402 (M+1).

COMPOUND BMM-3



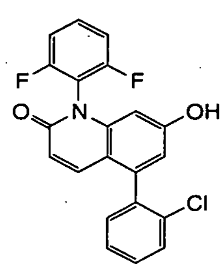
The title compound was was prepared similarly as **EXAMPLE PPP1**. Mass spectrum (ESI), 398 (M+1).

COMPOUND BMM-4



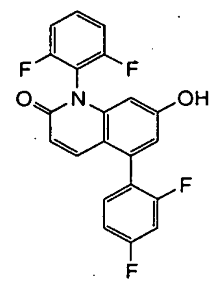
The title compound was prepared similarly as **EXAMPLE PPP1**. Mass spectrum (ESI), 400 (M+1).

COMPOUND BMM-5



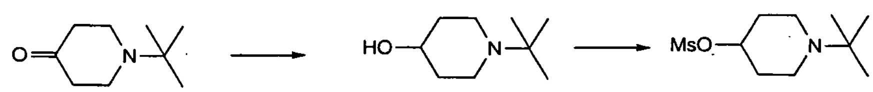
The title compound was prepared similarly as **EXAMPLE PPP1.** Mass spectrum (ESI), 384 (M+1).

COMPOUND BMM-6



The title compound was prepared similarly as **EXAMPLE PPP1.** Mass spectrum (ESI), 386 (M+1).

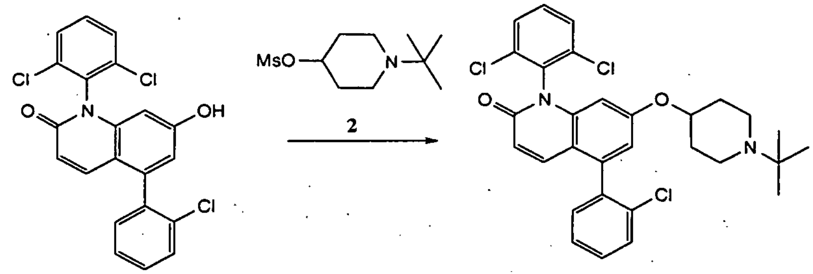
COMPOUND CMM-1



1 **2** **3**

To a solution of compound **1** (2.06g, 13.3mmol) in 15mL THF was added LAH (1m in THF) (15mL, 15mmol), and the solution was stirred for 0.5h at 0°C. To it was added slowly 1mL of 1M NaOH and filtered through a plug Celite. After removal of solvent, it was afford compound **2**(white solid). Mass spectrum (ESI) for **2**, 158 (M+1). The reaction mixture of compound **2** (1.75g, 11.13mmoL), triethylamine(2.5mL, 17.81mmol) and methanesulfonyl chloride (1.53g, 13.36mmoL) were stirred at 0°C for 1h. Then it was poured into 100mL of ether and 20mL of aq $NaHCO_3$ and extracted with ether (30mL x 3). The combined organic layer was dried over Na_2CO_3 and concentrated to afford white solid. Mass spectrum (ESI) for **3**, 236 (M+1).

EXAMPLE CMM1

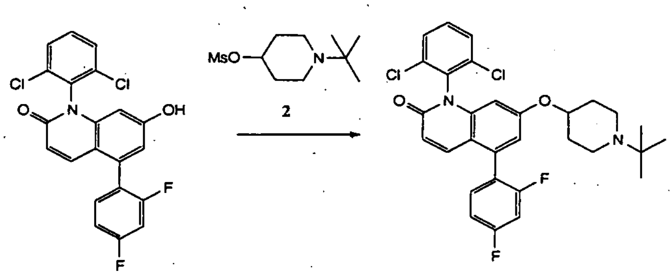


1

3

The mixture of compound **1** (126mg, 0.3mmol) and sodium hydride (60%) (12mg, 0.3mmol) in 6mL of DMF was stirred for 1h at rt. Then the compound **2** (78mg, 0.33mmol) was added and stirred for 12h at 135°C. Potassium carbonate (83mg, 0.6mmol) and compound **2** (78mg, 0.33mmol) was again added to the reaction mixture and stirred for another 24h at 135°C. After removal of solvent, it was poured in to 30mL of ethyl acetate and 10mL of aq Na_2CO_3, and it was extracted with ethyl acetate (15mL x 3). The combined organic layer was dried over Na_2CO_3 and concentrated. After removal of solvent, the residue was purified by TLC with hexane/ethyl acetate/2N NH_3 in MeOH to afford compound **3** (white solid). Mass spectrum (ESI) for **3**, 555 (M+1) and 557 (M+3).

EXAMPLE CMM2

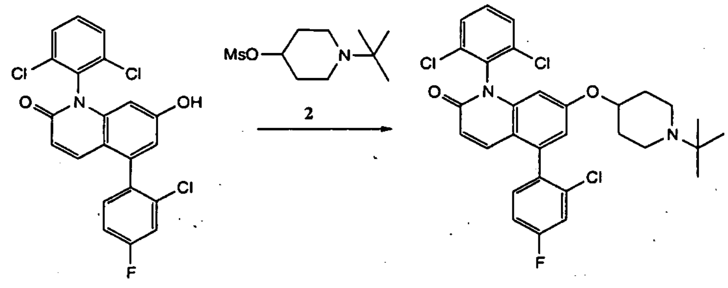


1

3

Mass spectrum (ESI) for **3**, 557 (M+1) and 559 (M+3).

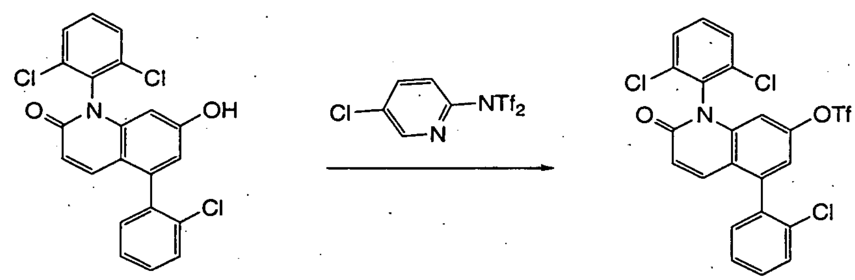
EXAMPLE CMM3



1 3

Mass spectrum (ESI) for **3**, 573 (M+1) and 575 (M+3).

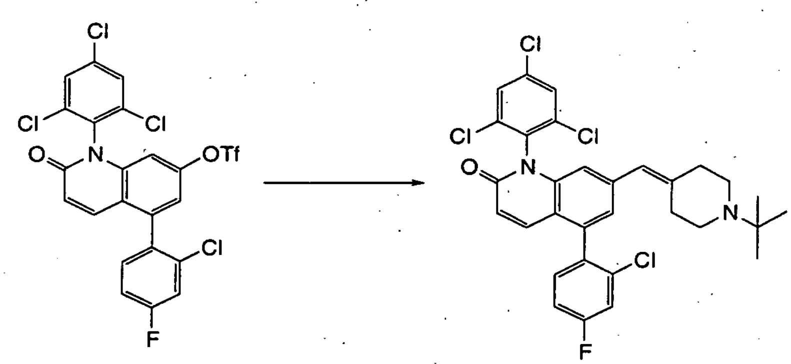
COMPOUND CMM-2



1 2

Mass spectrum (ESI) for **2**, 548 (M+1) and 550 (M+3).

EXAMPLE CMM4

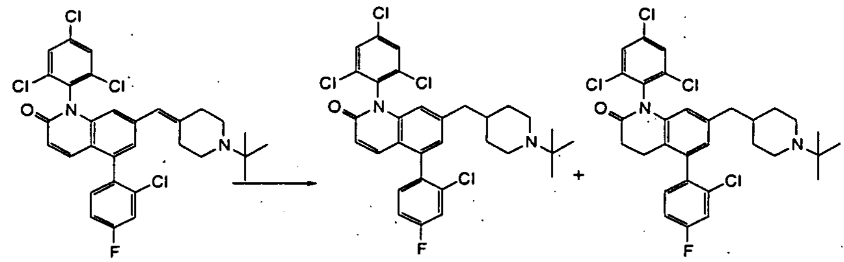


1 2

Mass spectrum (ESI) for **2**, 604 (M+1) and 606 (M+3).

EXAMPLE CMM5

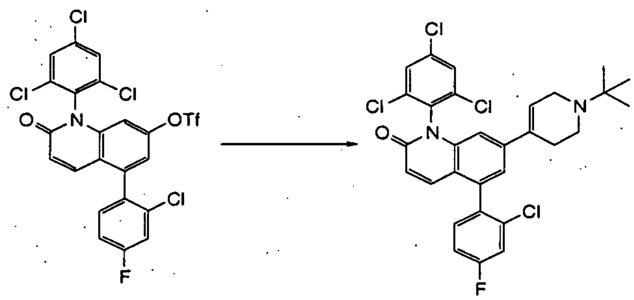
and EXAMPLE CMM6



1 2 3

Mass spectrum (ESI) for 2 **(EXAMPLE CMM5**, 606 (M+1) and 608 (M+3). Mass spectrum (ESI) for **3 (EXAMPLE CMM6)**, 608 (M+1) and 610 (M+3).

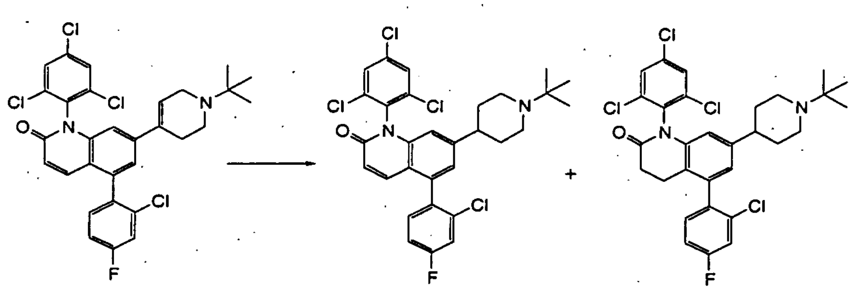
EXAMPLE CMM7



1 2

Mass spectrum (ESI) for **2**, 590 (M+1) and 592 (M+3).

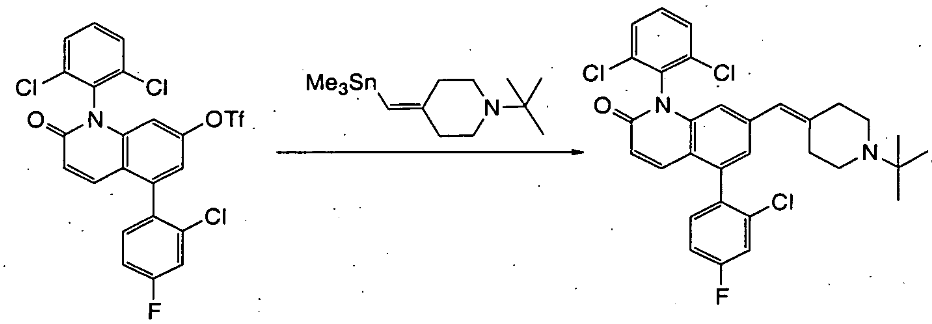
EXAMPLE CMM8
and EXAMPLE CMM9



1 2 3

Mass spectrum (ESI) for **2 (EXAMPLE CMM8)**, 592 (M+1) and 594(M+3). Mass spectrum (ESI) for **3 (EXAMPLE CMM9)**, 594 (M+1) and 596 (M+3).

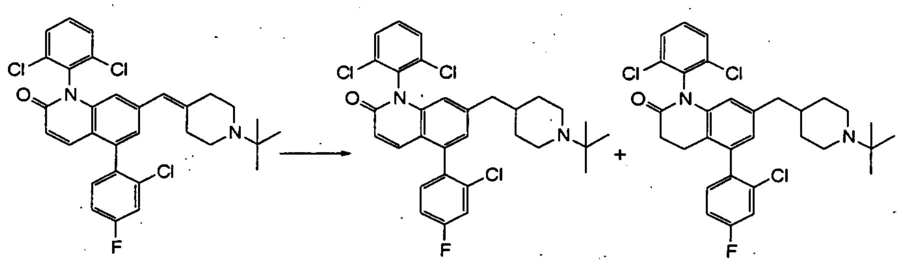
EXAMPLE CMM10



1 **2**

Mass spectrum (ESI) for **2**, 569 (M+1) and 571 (M+3).

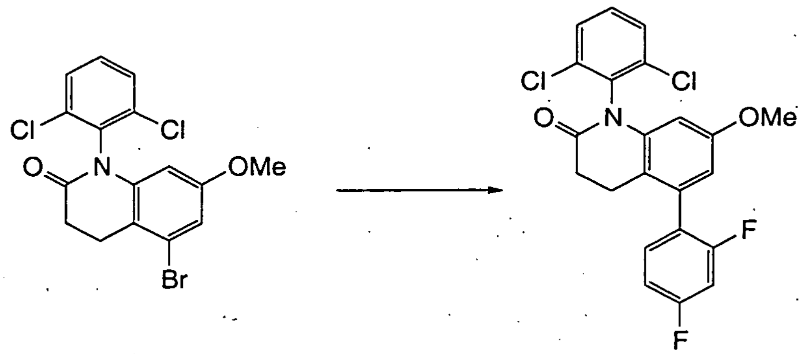
EXAMPLE CMM13 and
EXAMPLE CMM11



1 **2** **3**

Mass spectrum (ESI) for **2 (EXAMPLE CMM13)**, 571 (M+1) and 573 (M+3). Mass spectrum (ESI) for **3(EXAMPLE CMM11)**, 573 (M+1) and 575 (M+3).

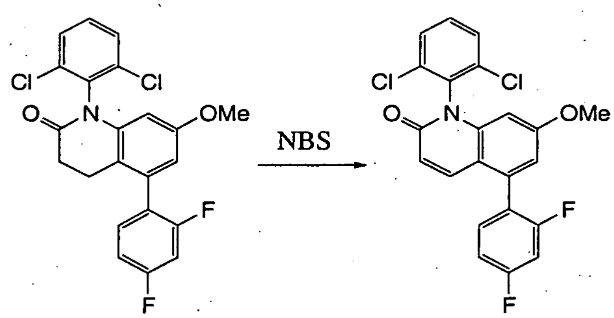
COMPOUND CMM-A9



1 2

Mass spectrum (ESI) for **2**, 434 (M+1) and 436 (M+3).

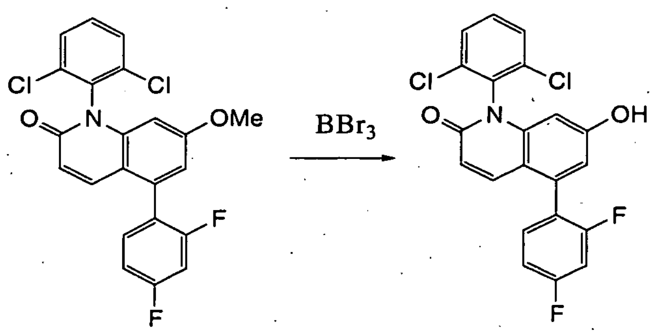
COMPOUND CMM-9



1 2

Mass spectrum (ESI) for **2**, 432 (M+1) and 434 (M+3).

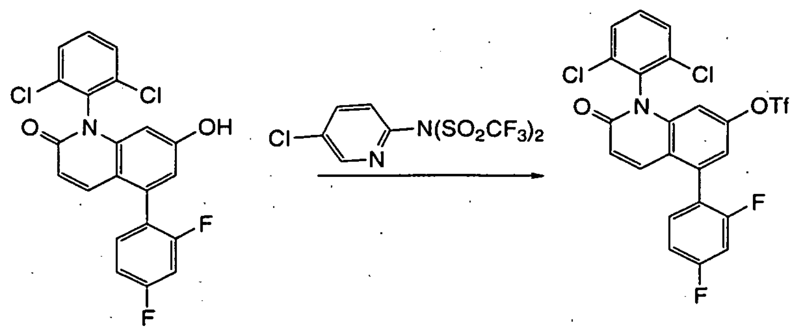
COMPOUND CMM-10



1 2

Mass spectrum (ESI) for **2**, 418 (M+1) and 420 (M+3).

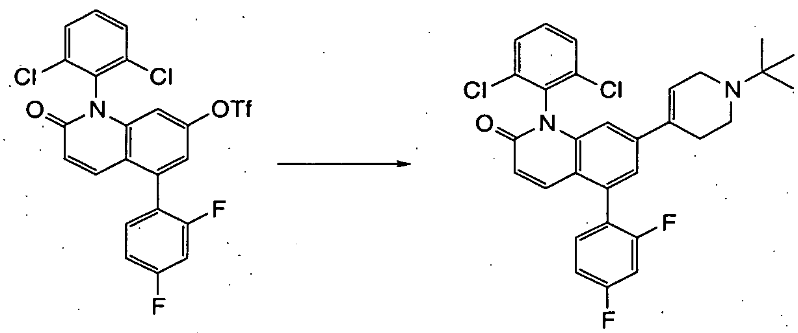
COMPOUND CMM-11



1 **2**

Mass spectrum (ESI) for **2**, 549 (M+1) and 551 (M+3).

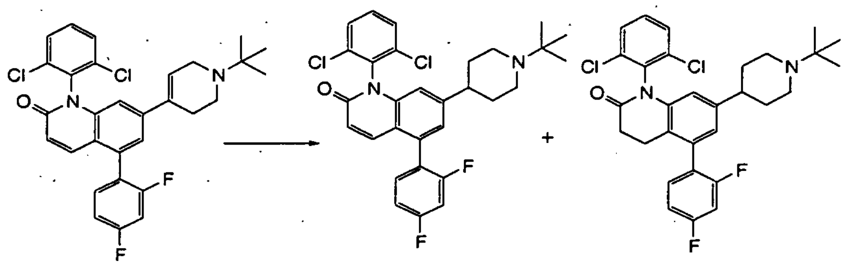
EXAMPLE CMM16



1 **2**

Mass spectrum (ESI) for **2**, 539 (M+1) and 541 (M+3).

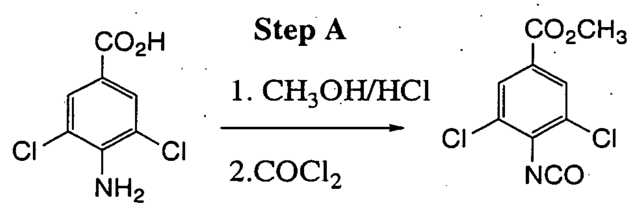
EXAMPLE CMM17 and
EXAMPLE CMM18



1 **2** **2**

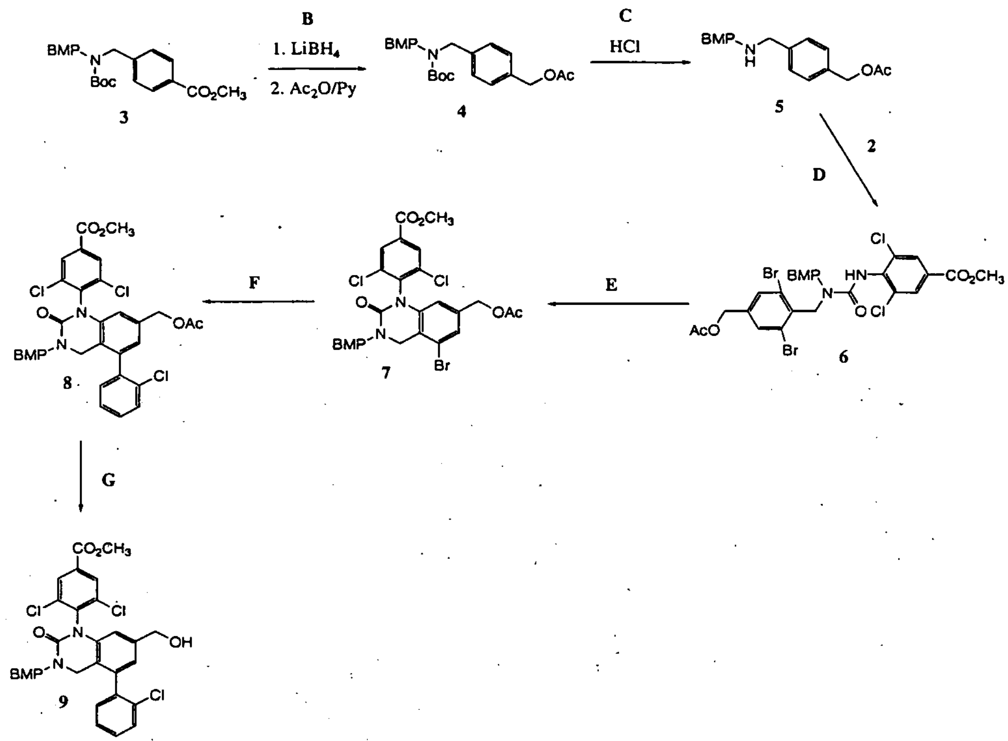
Mass spectrum (ESI) for **2 (EXAMPLE CMM17)**, 541 (M+1) and 543 (M+3). Mass spectrum (ESI) for **3 (EXAMPLE CMM18)**, 543 (M+1) and 545 (M+3).

COMPOUND DMM-1



1 **2**

Step A: To a solution of **1** (8.06g, 39.1mmol) in 150mL of methanol was added 20mL of HCl in dioxane (C = 4M) and the mixture wash heated at reflux for 5h. Volatiles were removed, dissolved in CH_2Cl_2, washed once with $NaHCO_3$, dried with Na_2SO_4 and filtered through a plug of silica gel to yield a solid. It was dissolved in 100mL of THF and was added 100mL of $(COCl)_2$ in toluene (20% weight). The solution was heated to reflux for 3h. All volatiles were removed to give a yellow solid, which was used in next step directly.



Step B: A solution of **3** (13.96g, 25.70mmol) in 60mL of THF was added LiBH4 (37.7mL, as 2M solution in THF) and the solution was stirred at rt for 45h. The reaction was quenched with 20mL of water and was removed of THF by vacuum. The residue was dissolved in CH_2Cl_2, washed with $NaHCO_3$, dried with Na_2SO_4. Upon removal of solvent, the residue was dissolved in 30mL of pyridine and was added acetic anhydride (4.83mL, 51.2 mmol). After 3h at rt, volatiles were removed by vacuum, the residue was dissolved in ether and was washed by $NaHCO_3$ and brine, dried by Na_2SO_4 and filtered to give **4.**

StepC: A solution of **4** (14.44g, 25.6mmol) in 100mL of CH_2Cl_2 was added to 25.6mL of HCl in dioxane (C = 4M). After 18h, it was removed of volatiles and was dissolved in CH_2Cl_2, washed with NaOH and taken to next step.

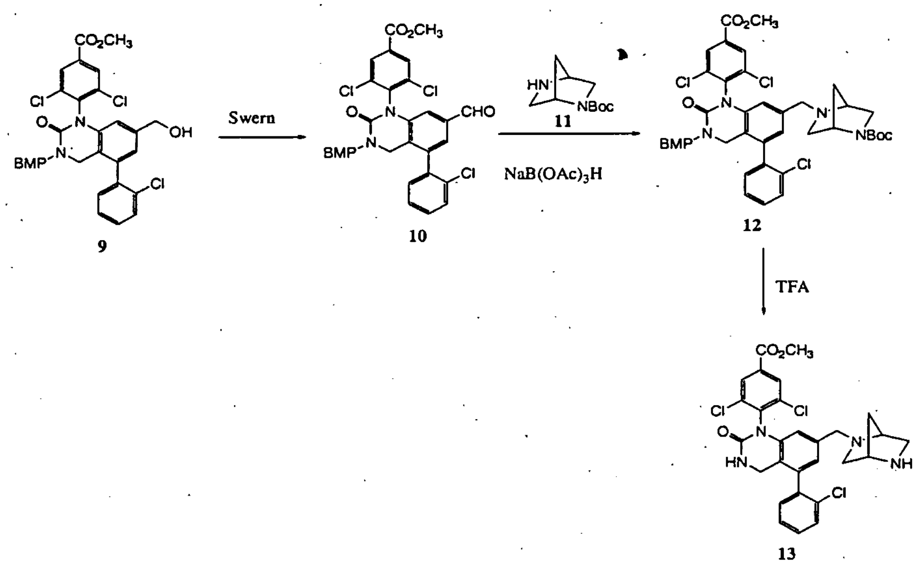
Step D: A solution of **5** in 100mL of CH_2Cl_2 was added Et_3N (4.28mL, 30.72mmol) and **2** (26.88mmol) in 27mL of CH_2Cl_2. After 16h at rt, it was loaded on silica gel and eluted with EtOAc:hexane = 1:3 give **6** (16.62g). Mass spectrum (ESI) for 6, 703 (M+1).

Step E: This reaction was carried out similarly to procedures described above to give 7. Mass spectrum (ESI) for **7**, 622 (M+1).

Step F: This Suzuki reaction was carried out with standard conditions. Mass spectrum (ESI) for **8**, 654 (M+1).

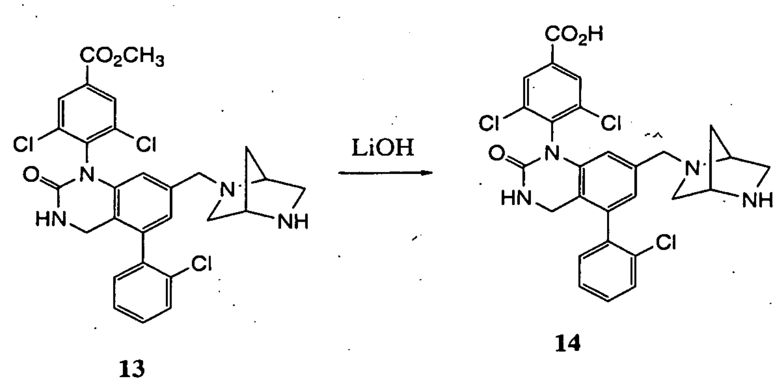
Step G: A solution of **8** in 10mL of CH_2Cl_2 (1.2235g) was added K_2CO_3 (50mg) and 40mL of MeOH and the solution was heated at 45^{o}C for 4h. Volatiles were removed and the residue was purified by flash chromatography EtOAc/hexane = 3:7 to give **9**. Mass spectrum (ESI) for **9**, 613 (M+1).

EXAMPLE DMM1



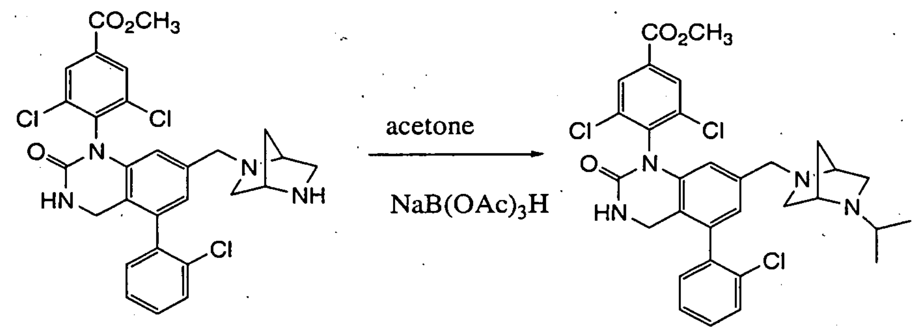
Compound **9 (COMPOUND DMM-1)** was converted to aldehyde **10** via standard Swern reaction. Aldehyde **10** was coupled with amine **11** via $NaB(OAc)_3H$ to afford **12**. Treatment of **12** with TFA afford **13 (EXAMPLE DMM1)**. Mass spectrum (ESI) for **13**, 573 (M+1).

EXAMPLE DMM2



A solution of **13 (EXAMPLE DMM1)** (31.1 mg, 0.054 mmol) in 1.5mL of MeOH was added 0.5mL of water and $LiOH.H_2O$ (11.4 mg, 0.27 mmol). The solution was stirred at rt for 2 h and was purified by reversed phase HPLC to give **14**. Mass spectrum (ESI) for **14 (EXAMPLE DMM2)**, 559 (M+1).

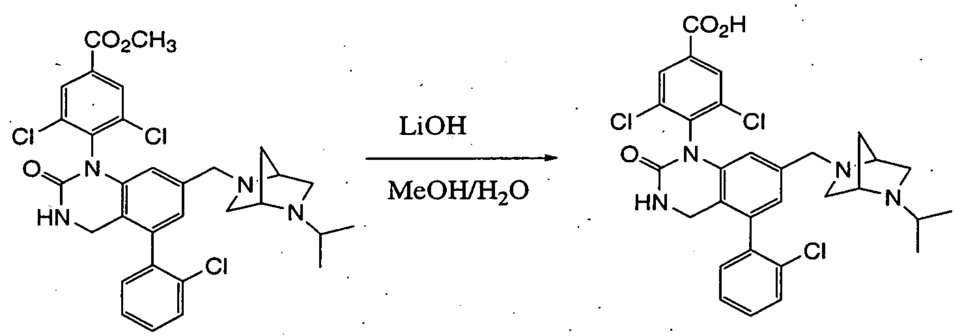
EXAMPLE DMM3



14 **15**

A solution of **14 (EXAMPLE DMM2)** (0.27g, 0.47mmol) and $NaB(OAc)_3H$ (0.20g, 0.94mmol) in CH_2Cl_2 was added acetone (0.34mL, 4.7mmol) and the mixture was stirred for 16h at rt. It was diluted with CH_2Cl_2, washed with $NaHCO_3$, dried with Na_2SO_4 and filtered through Celite. Removal of solvent give **15 (EXAMPLE DMM3)**. Mass spectrum (ESI) for **15**, 615 (M+1).

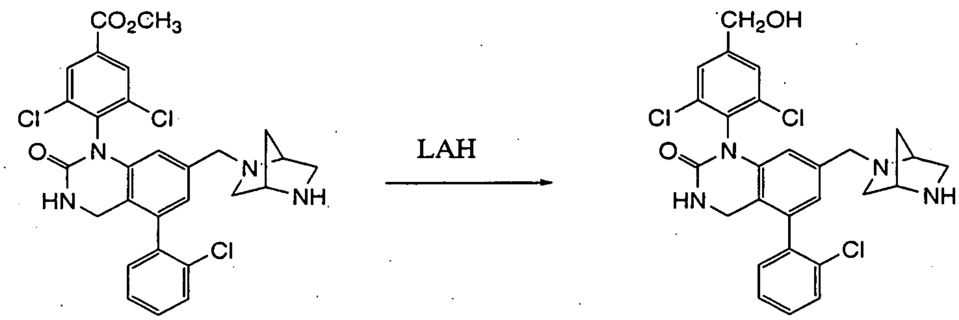
EXAMPLE DMM4



15 **16**

This reaction was carried out as **EXAMPLE DMM3** to give **16 (EXAMPLE DMM4)** as TFA salt. Mass spectrum (ESI) for **16**, 601 (M+1).

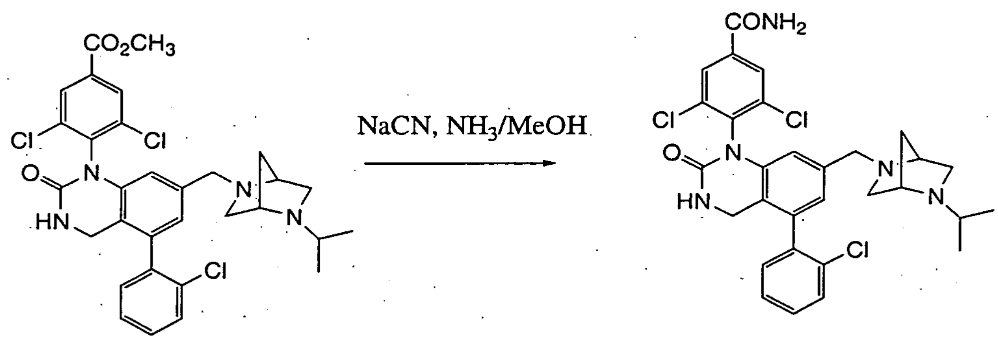
EXAMPLE DMM5



14 17

A solution of **14 (EXAMPLE DMM2)** (30.8mg, 0.050mmol) in 2.5mL of THF was added LAH (0.090mL as 1M THF solution) at 0°C. After 30min, it was quenched with 2 drops of water. After 5min, Na_2SO_4 was added to remove excess water and filtered through Celite. The residue was purified by reversed phase HPLC to give **17 (EXAMPLE DMM5)** as TFA salt. Mass spectrum (ESI) for **17**, 543 (M+1).

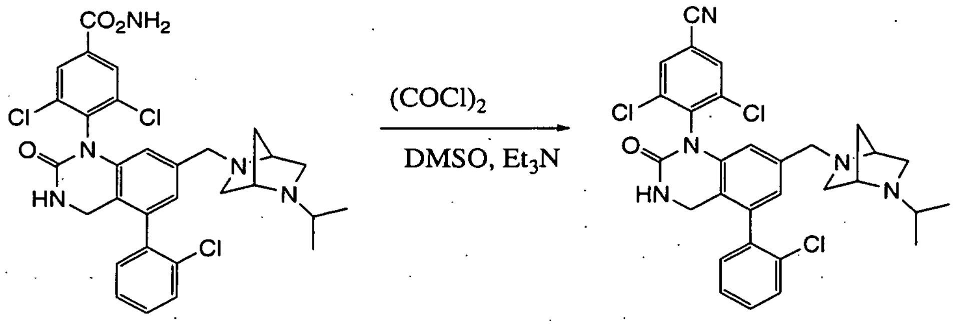
EXAMPLE DMM6



15 18

A solution of **15 (EXAMPLE DMM3)** (0.17g, 0.28mmol) in 5mL of 2M NH_3 in MeOH was added NaCN (10mg, 0.20 mmol) and was heated at 50°C for 5h. Volatiles were removed and the residue was purified by reversed phase HPLC to give **18 (EXAMPLE DMM6)**. Mass spectrum (ESI) for **18**, 598 (M+1).

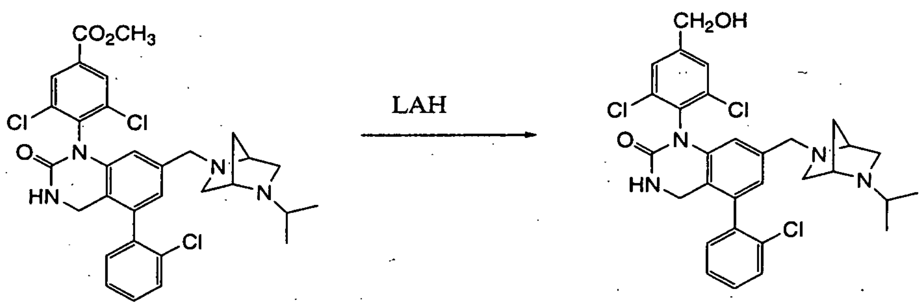
EXAMPLE DMM7



18 19

This reaction was carried out under standard Swern reaction conditions. The crude was purified by HPLC to give **19 (EXAMPLE DMM7)** as TFA salt. Mass spectrum (ESI) for **19**, 580 (M+1).

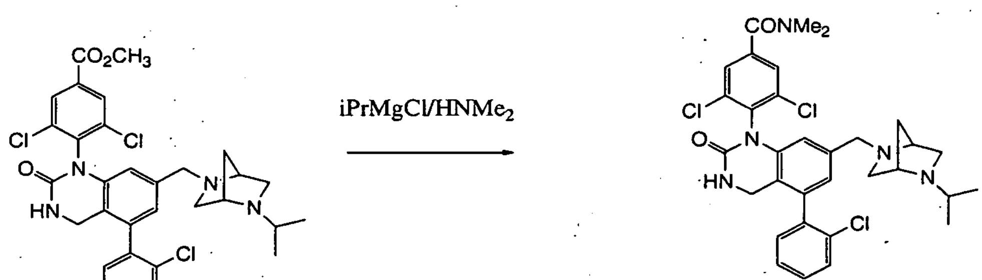
EXAMPLE DMM8



15 20

This reaction was carried out as **EXAMPLE DMM5** to give **20 (EXAMPLE DMM8)**. Mass spectrum (ESI) for **20**, 585 (M+1).

EXAMPLE DMM9

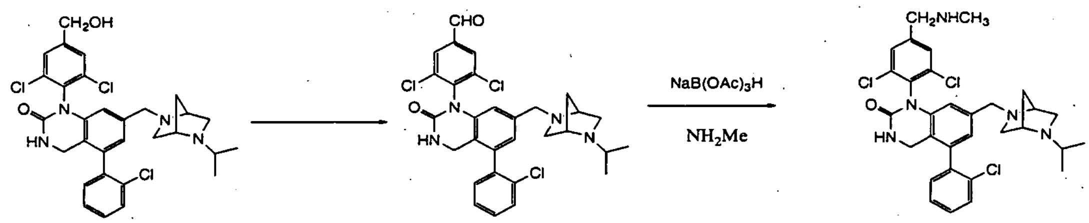


21

15

A solution of **15** (EXAMPLE DMM3) (32.6mg, 0.053mmol) and dimethylamine (0.053mL, 0.106mmol) in 2mL of THF was added iPrMgCl (0.080mL, 0.159mmol) at –20°C. The solution was warmed up to –10°C over 40min and was quenched with 2 drops of water. It was diluted with 10mL of CH_2Cl_2 and filtered through celite. The crude was purified by HPLC to give **21 (EXAMPLE DMM9)** as TFA salt. Mass spectrum (ESI) for **21**, 626 (M+1).

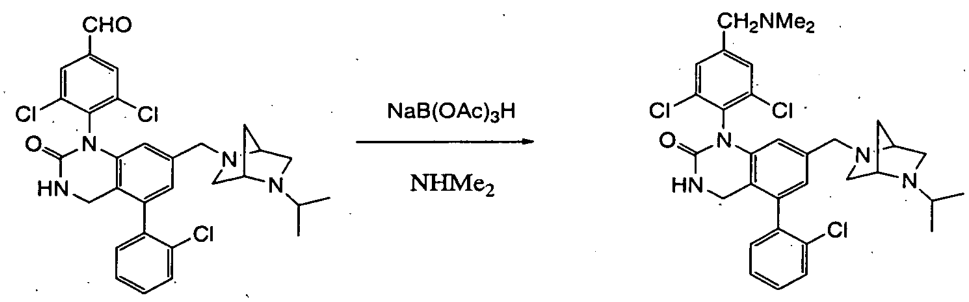
EXAMPLE DMM10



20 22 23

Step A: **22** was obtained via standard Swern reaction conditions.
Step B: The reaction was carried out as **EXAMPLE DMM3**. Mass spectrum (ESI) for **23 (EXAMPLE DMM10)**, 598 (M+1).

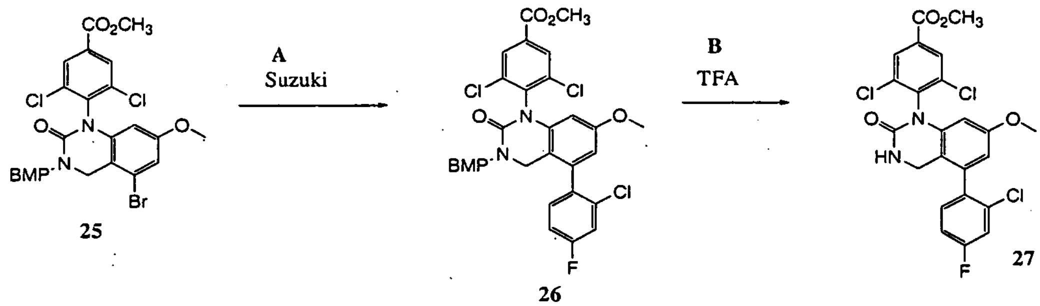
EXAMPLE DMM11



22 24

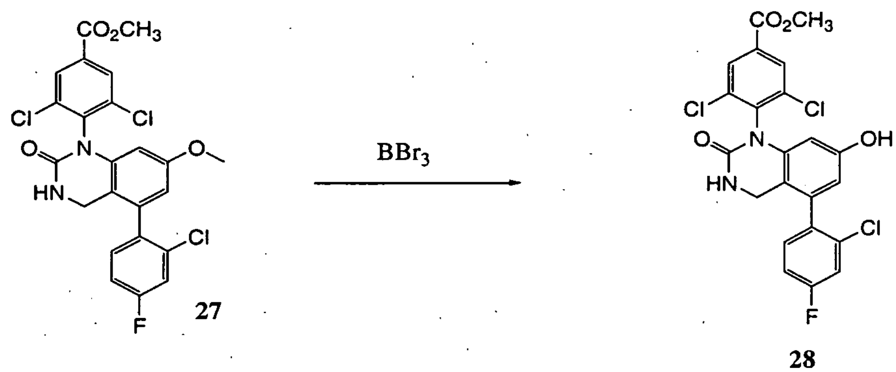
The reaction was carried out as **EXAMPLE DMM3**. Mass spectrum (ESI) for **24 (EXAMPLE DMM11)**, 612 (M+1).

COMPOUND DMM-2



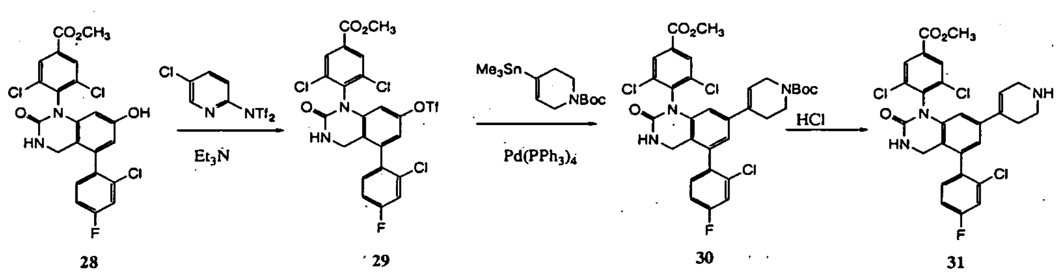
Step A: This reaction was carried via standard Suzuki conditions to give **26**.
Step B: The PMB group of **26** was removed via treatment of TFA. The crude was purified by flash chromatography (EtOAc: hexane = 3:7) to give **27 (COMPOUND DMM-2)**. Mass spectrum (ESI) for **27**, 509 (M+1).

COMPOUND DMM-3



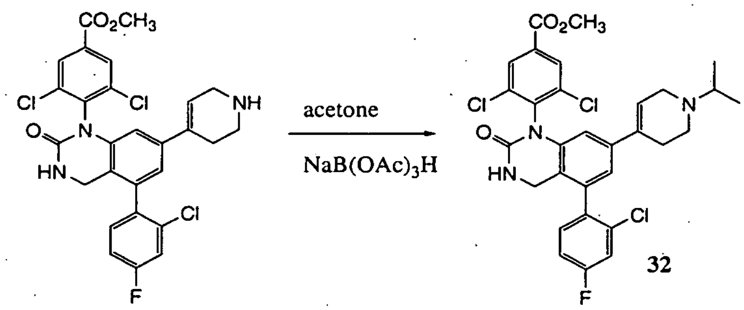
This reaction was carried out similarly to procedures described above. Mass spectrum (ESI) for **28 (COMPOUND DMM-3)**, 495 (M+1).

EXAMPLE DMM12



Compound **31 (EXAMPLE DMM12)** was prepared from **28 (COMPOUND DMM-3)** through the standard steps in the scheme. Mass spectrum (ESI) for **31**, 560 (M+1).

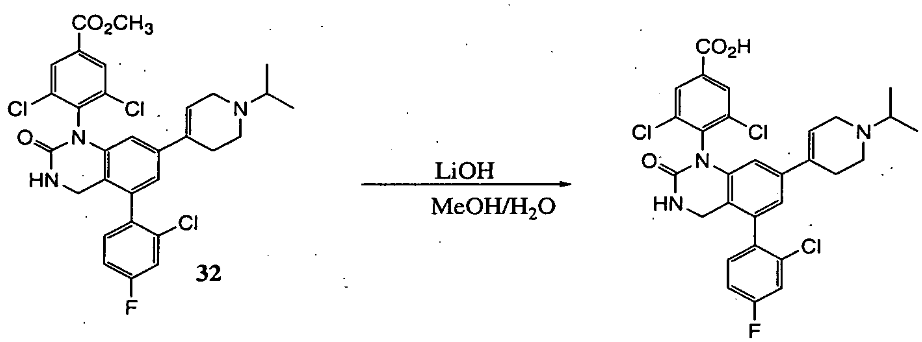
EXAMPLE DMM13



31 **32**

This reaction was carried out as **EXAMPLE DMM3**. Mass spectrum (ESI) for **32 (EXAMPLE DMM13)**, 602 (M+1).

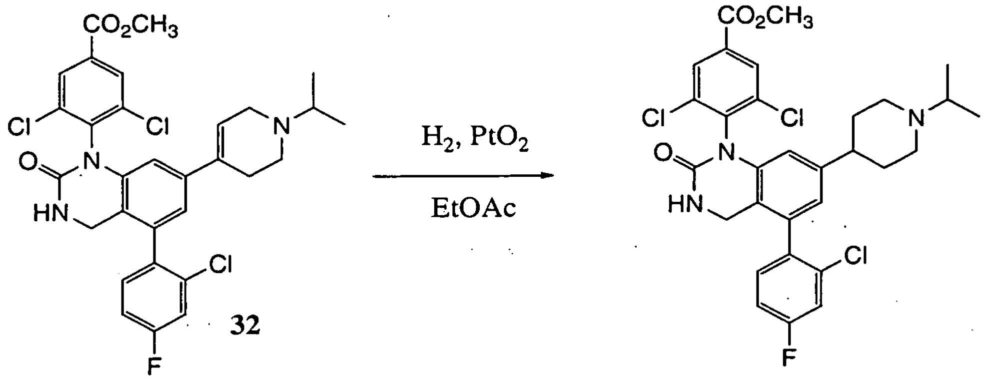
EXAMPLE DMM14



32 **33**

This reaction was carried out similarly to that described for **EXAMPLE DMM4**. Mass spectrum (ESI) for **33 (EXAMPLE DMM14)**, 588 (M+1).

EXAMPLE DMM15

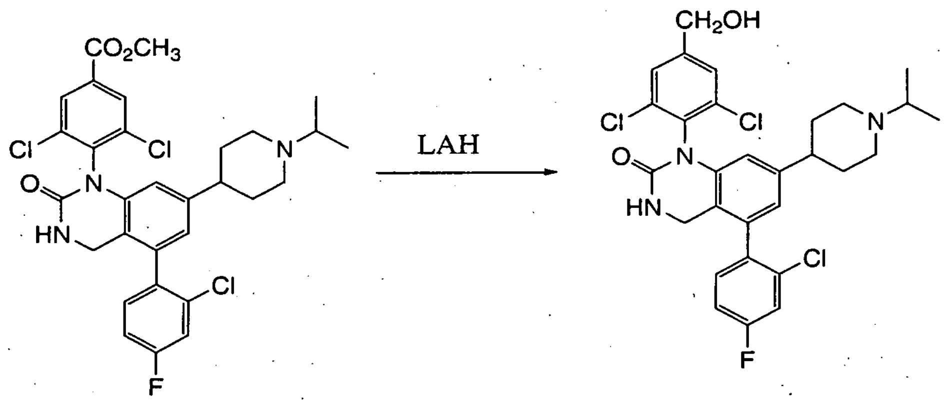


32

34

This reaction was carried out with 32psi of H_2 for 16h in EtOAc. Mass spectrum (ESI) for **34 (EXAMPLE DMM15)**, 604 (M+1).

EXAMPLE DMM16

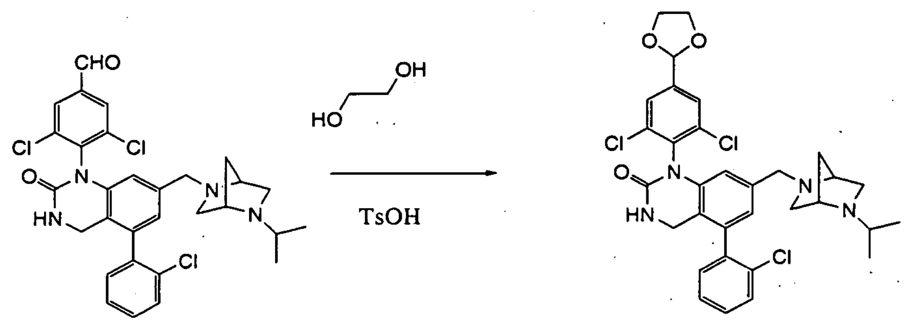


34

35

This reaction was carried out similarly to procedures described above. Mass spectrum (ESI) for **35 (EXAMPLE DMM16)**, 576 (M+1).

EXAMPLE DMM17

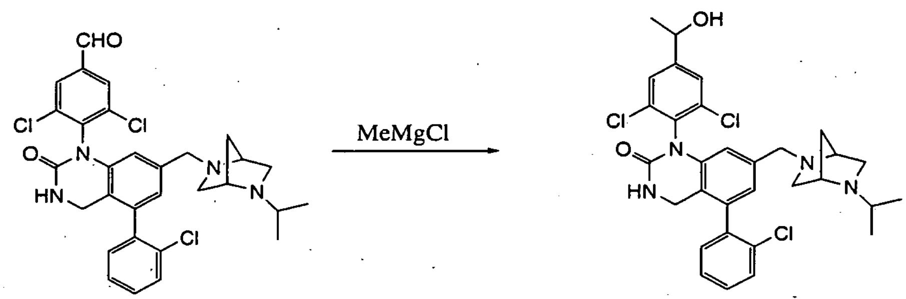


22

36

A solution of **22** from **EXAMPLE DMM10** (33.2mg, 0.057mmol) and ethylene glycol (0.032mL, 0.57mmol) in 2.5mL of benzene was added TsOH.H_2O (26mg, 0.14mmol) and was heated at reflux for 1h. Volatiles were removed and the crude was purified by HPLC to give **36 (EXAMPLE DMM17)** as a TFA salt. Mass spectrum (ESI) for **36**, 627 (M+1).

EXAMPLE DMM18

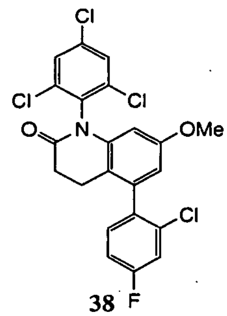


22

37

A solution of **22** from **EXAMPLE DMM10** (95.2mg, 0.163mmol) in 4mL of THF was added MeMgCl (0.16mL, 3M solution in THF) at rt. After 1.5h, it was quenched with 3 drops of water and was filtered through celite. The crude was purified by HPLC to give **37 (EXAMPLE DMM18)** as a TFA salt. Mass spectrum (ESI) for **37**, 599 (M+1).

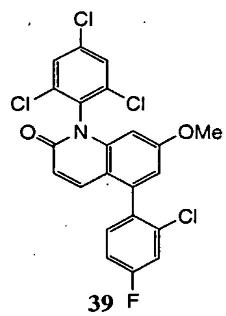
COMPOUND DMM-4



38

Mass spectrum (ESI) for **38**, 484 (M+1).

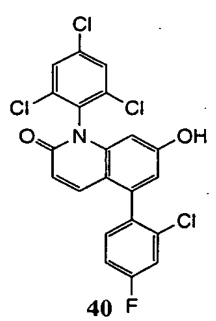
COMPOUND DMM-5



39

Mass spectrum (ESI) for **39**, 482 (M+1).

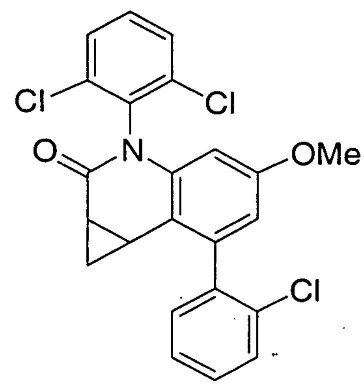
COMPOUND DMM-6



40

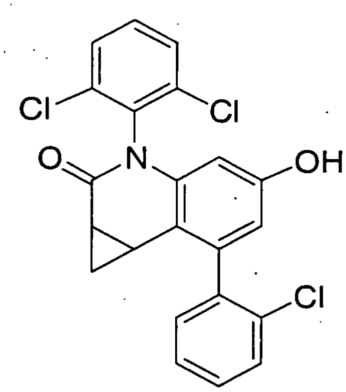
Mass spectrum (ESI) for **40**, 468 (M+1).

Compound CN-1



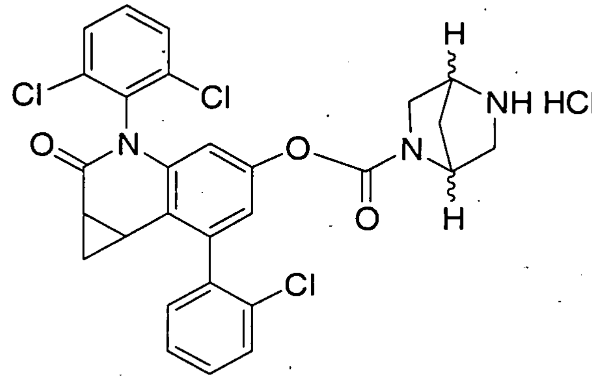
Oil free sodium hydride (36mg) suspended in dry DMSO (5mL) was added trimethylsulfoxonium chloride (193mg) at rt. After bubbling subsided, the **INTERMEDIATE 8** (300mg) in DMSO (5mL) was added to reaction mixture. The solution was stirred at rt for 1h and at 60C for 18h. The mixture was partitioned between ethyl acetate and water. The two layers were separated and the organic phase was washed with water (3x), brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel (hexanes/ethyl acetate=2/1) to give title compound. ^{1}H NMR($CDCl_3$, 500MHz, diastereomers): 7.53 (m, 3H), 7.39 (m, 4H), 6.53 (d, 1H, one diastereomer), 6.48 (d, 1H, one diastereomer), 5.70(d, 1H, diastereomers mixture), 3.68 (s, 3H, one diastereomer), 3.51 (s, 3H, one diastereomer), 2.20 (m, 2H), 1.65 (m, 1H), 1.07 (m, 1H, one diastereomer), 0.97 (m, 1H, one diastereomer). MS(ES) 444 (M+H).

Compound CN-2



The title compound was prepared as described in **INTERMEDIATE 3**. MS(ES) 430 (M+H).

EXAMPLE CN-1



To a solution of **Compound CN-2** (43mg) in dichloromethane was added diisopropylethylamine (0.17mL) and phosgen (0.5mL, 1.9M in toluene)at – 20C. The mixture was warmed up to rt and stirred for 16h. The solution was concentrated to dry to give crude mixture. To a solution of this crude mixture in dichloromethane was added t-butyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and diisopropylethylamine at rt and stirred for 16h. Removal of the solvent and subsequent purification by preparative thin layer chromatography (hexanes/ethyl acetate=2/1) provided the coupling product. The coupling product in ethyl acetate at 0C was bubbled though hydrogen chloride gas until saturation occurred. The reaction was stirred for 15min, until thin layer chromatography analysis indicated that the reaction was complete. The solution was concentrated to remove the ethyl acetate. The residue was the redissolved in dichloromethane and hexanes was added followed by evaporation in vacuo to afford the title product as a solid. ^{1}H NMR(CD_3OD, 500MHz, mixture of diastereomers): 7.64-7.42 (m, 7H), 6.81 (m, 1H), 5.94 (m, 1H), 4.45 (s, 1H), 3.67 (s, 1H), 3.52 (m, 1H), 3.42 (m, 1H), 2.38-2.15 (m, 4H), 1.78-1.62 (m, 1H), 1.37 (m, 2H), 0.95 (m, 1H). MS(ES) 556 (M+H).